HYPOTENSIVE DRUGS

HYPOTENSIVE DRUGS

Proceedings of a symposium on hypotensive drugs and the control of vascular tone in hypertension, held in London on April 5th and 6th, 1956 at the Wellcome Foundation

Edited by

M HARINGTON
MB MRCP

PERGAMON PRESS LONDON & NEW YORK

LIST OF SPEAKERS AND OPENERS OF DISCUSSIONS

PROF C BARTORELLI Viale Piare 20 Milan Siena Italy
MR J W BILLINGHURST Wellcome Research Laboratories Beckenham Kent
DR H BLASCHKO Department of Pharmacology University of Oxford
J CONWAY Charing Cross Hospital Medical School Department of Physiology London
R S DUFF Department of Cardiology St Bartholomew s Hospital London
M A FLOYER, Medical Unit The London Hospital Medical College Turner Street E 1
B FOLKOW Department of Physiology University of Gothenburg Sweden
MR. A F GREEN Wellcome Research Laboratories Beckenham Kent
SIR CHARLES HARRINGTON F R S National Institute for Medical Research Mill Hill London
DR M HARINGTON University College Hospital London
DR B HOOD Medical Clinic I University of Gothenburg Sweden
DR H R. ING F R S Department of Pharmacology University of Oxford
J M LEDINGHAM Medical Unit The London Hospital Medical College Turner Street E 1
PROF H McILWAIN Biochemical Department Institute of Psychiatry Maudsley Hospital S E 5
J McMICHAEL Postgraduate Medical School of London Ducane Road W 12
DR W S PEART Medical Unit St Mary s Hospital London
PROF G A PERERA Department of Medicine Columbia University College of Physicians and Surgeons New York
PROF F H SMIRK Department of Medicine Otago University Medical School Dunedin N Z
DR J TRIPOD Ciba Ltd Basle Switzerland
DR MARTHE VOGT F R S Pharmacology Department University of Edinburgh

Published by The Pergamon Press
4 & 5 Fitzroy Square, London W 1

Printed in Great Britain by Page Bros (Norwich) Ltd

CONTENTS

DR J G WIDDICOMBE Department of Pharmacology St Bartholomew s Hospital London
PROF C WILSON, Medical Unit London Hospital
DR ELEANOR ZAIMIS, Department of Pharmacology, Royal Free Hospital School of Medicine, London

3RD SESSION

CLINICAL APPLICATIONS OF HYPOTENSIVE DRUGS

4TH SESSION

THE CONTROL OF VASCULAR TONE IN HYPERTENSION

OPENING REMARKS

SIR CHARLES HARINGTON F R S

I ASSUME that I have been asked to say a word or two in opening this symposium primarily because I happen to be chairman of a committee of the Biological Council at whose instance the idea of this symposium was first mooted This committee which owes its existence in the first place to the initiative of our chairman at this morning's session Professor BERGEL has assumed the task of examining the general field of research on drug action and suggesting from time to time subjects within that field which are ripe for general discussion and subjects which require for discussion the members of more than one scientific society It is of course the hope of the committee that such discussions will not only be informative of the present state of development but will point the way to further progress

The suggestions that are put forward by this committee can only be brought to fruition through the action of the relevant scientific societies and it is most encouraging that in so many cases the suggestions that have been made have in fact proved acceptable to one or another society

It has been most gratifying also that when there has been need for help in the organization of these symposia beyond the scope of the scientific societies this help has been forthcoming This is I think the third occasion on which the Wellcome Foundation has shown the greatest generosity in offering hospitality without which neither this meeting nor the previous ones on histamine and anticholinesterase could have been so pleasantly and so satisfactorily arranged we must all feel deeply grateful to the foundation for their action We can only hope they will feel rewarded by the scientific value of the discussions which are to take place

The fact that it has been thought worth while to organize this particular meeting is an illustration of the advances that have been made in this particular branch of pharmacology and therapeutics and also of the urgency of the medical problem of the control of vascular tone in hypertension

The actual programme illustrates well the present state of affairs in which some progress has been made towards the solution of the

PREFACE

THIS Symposium on Hypotensive Drugs and the Control of Vascular Tone in Hypertension was held at the instigation of the Biological Council s Co ordinating Committee for Symposia on Drug Action The work of this committee is described by its chairman, Sir Charles Harington in his opening remarks It has been responsible for a series of symposia of which this is the third two previous ones have dealt with anticholinesterases and with histamine

The present symposium originated in a suggestion by Professor F Bergel It was supported by the following scientific societies the British Pharmacological Society, the Physiological Society, the Royal Society of Medicine (*Section of Experimental Medicine and Therapeutics*) the Fine Chemicals Group, S C I, the Biochemical Society the Pharmaceutical Society the Association of Anaesthetists, and the Society for Endocrinology Representatives of these societies formed an organizing committee whose members were Dr H J Barber Professor F Bergel Dr G R Boyes Dr T M Chalmers Dr C Dalgleish Dr A C Dornhorst Professor W D M Paton Professor F T G Prunty Dr H O Schild Dr J B Wyman and Dr Eleanor Zaimis The detailed planning was carried out by a working subcommittee consisting of Dr Schild, Dr Dornhorst, Professor Paton, and Dr Zaimis

The organizers wish to acknowledge the generosity of the Wellcome Foundation and in particular Dr Adamson who provided facilities for the symposium thus enabling 250 people to attend and who also extended hospitality to visitors from overseas Accommodation for visitors was al o given by the Ciba Foundation The editor acknowledges gratefully the co operation he has had in the publication of this volume from the Pergamon Press Finally all concerned with planning the symposium would like to express their deep debt to Dr Eleanor Zaimis who herself carried out the major part of the organization and who did more than anyone else to make the symposium a success for those who attended

the unexpected and powerful ganglionic blocking action of the hexamethylene salt and it is this discovery which is the real basis for this symposium

The point I wish to make is I think a fairly obvious one KING s work on curare wherever and with whatever object it had been done would have stood in its own right as a considerable scientific achievement under less favourable circumstances however this work might have remained on record only as a classical exercise in organic chemistry Similarly a pharmacological investigation of the methonium series restricted to the search for compounds with muscle relaxing properties would have concentrated attention on decamethonium and although this might in turn have led to the interesting physiological synthesis of the mode of action of this drug which Dr ZAIMIS carried out with such skill the more important properties of the hexamethonium salt might well have passed unobserved It was only the sharing of the particular kinds of ch mical and pharmacological interest and knowledge between colleagues in the same building that produced the result which emerged on a basis of systematic research and in a reasonably short space of time I can assure you that it is events such as this which gladden the hearts of those who have to direct research institutes

I have spoken only in terms of methonium compounds because as I have said it is the work of these drugs that has made it worth while to hold this symposium However, we are now seeing the discovery of many other types of compound which are finding important places in the pharmacological control of vascular tone and the contributions to the pharmacology of reserpine that we shall hear will be particularly welcome Moreover we need not doubt that the views of th clinical members of the symposium on the practical usefulness of the various drugs now available will certainly be interesting and may be salutary to the pharmacologists

In conclusion I should like to reiterate my hope that this symposium will do more than present a synopsis of current knowledge in the field of discussion We are most fortunate in the distinction of the members of the symposium who are to make scientific contributions These contributions will give an authoritative statement of the present position and should also bring out clearly the weaknesses of the situation and the aspects on which more work is required With good fortune they may also produce some ideas on the directions which further work should follow and as to the best means of attack on the outstanding problems If the symposium attains these objects those who have been responsible for organizing it will be well rewarded

problem, but in which still more remains to be done After all, it is only within the last ten years or so that drugs have been discovered which are of real clinical value in the control of hypertension But, as so often happens when a discovery of this sort is made and a new field is opened up the number of drugs with therapeutic possibilities in this direction is now rapidly increasing

I personally, welcome the invitation to say a word or two on this occasion for two reasons, the first is that it gives me an opportunity of referring to the development of the earliest practically useful drugs, namely the methonium series which took place largely in the National Institute for Medical Research and in doing so of paying a tribute to the memory of my former colleague and friend HAROLD KING whose death we have had recently to mourn At the same time I am enabled to ride one of my own hobby horses in that the story of the development of the methonium drugs in so far as it concerned the National Institute seems to me to be a model example of the way in which things ought to happen but do not always happen in research institutes

In saying this of course, I do not for a moment mean to suggest that the credit for the development of the methonium drugs belongs entirely to the National Institute of Medical Research on the contrary much is owed to the work of others and particularly to that of Dr ING and his colleague Dr BARLOW who themselves synthesized a series of polymethylene bisquaternary ammonium salts their interest lying chiefly in the possible so called curare like action of such salts It was however the work of KING on the curare alkaloids which I think really opened the way to the systematic pharmacological work that has proved so profitable KING s research on curare was a masterly series of investigations extending over many years and leading from the isolation of d tubocurarine in the pure state to the determination of the constitution of this alkaloid This research might well not have been undertaken by him but for the inspiration of the interest in substances affecting nervous conduction and neuromuscular transmission which existed in Sir HENRY DALE s laboratory in the institute for so many years It was certainly this interest which led KING to speculate on the possibility of reproducing curare like activity in simple synthetic compounds and hence to encourage Dr ZAIMIS to synthesize a long series of polymethylene bisquaternary ammonium iodides It was again the same interest that ensured that these compounds received a thorough pharmacological investigation by KING s colleagues particularly by Dr PATON in collaboration with Dr ZAIMIS herself which revealed

1st SESSION

(MORNING)

THURSDAY APRIL 5th

Chairman Professor F Bergel

CHEMICAL AND BIOCHEMICAL ASPECTS

STRUCTURE ACTION RELATIONSHIPS OF HYPOTENSIVE DRUGS

H R ING

IN a recent review article Dr ZAIMIS (1955) referred to acetylcholine as a masterpiece among molecules because it activates so many different receptors I do not think that I can emulate this versatile molecule and elicit appropriate responses from all the members of so diverse an audience I may hope to activate some receptors by my remarks but I fear I may fail to excite and may even depress others

Hypotensive drugs are of many types differing both chemically and pharmacologically so that if I am to fulfil the wishes of the organizing committee I must hop as gracefully as I can from one group to another Moreover since I cannot deal fully with all the different groups the amount of space I devote to each group will be dictated by my personal interests

I will start with the veratrum alkaloids not because I have anything useful to say about their structure action relationships but because of the intrinsic interest of the mechanism of their hypo tensive effect the clue to which was discovered by VON BEZOLD and HIRT (1867) nearly a century ago At least seventeen alkaloids have been isolated from *Veratrum* spp or from sabadilla seeds (the commercial source) four alkamines two alkamine glucosides and eleven alkamine esters All the alkamines whether occurring naturally or obtained by hydrolysis of glucosidic or ester alkaloids contain 27 C atoms 1 tertiary N atom and 2–9 O atoms they are steroid alkamines containing six ring structures with the solitary N atom so far as we know common to two rings The structure of none of the alkamines is known with certainty although considerable advances have been made in elucidating the structure of the cevine group The ester alkaloids are the most potent of the group Vera tridine ($C_{36}H_{51}O_{11}N$) is a typical example it is hydrolysed at 0 to veratric acid ($C_9H_{10}O_4$) and veracevine ($C_{27}H_{43}O_8N$) and the latter is converted by less mild treatment with alkali first into cevagenine and then into cevine both isomeric with veracevine

The main interest of these alkaloids for my purpose lies in the

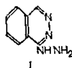
The activity appears to depend upon an intact amidine group since substitution of aryl or alkyl groups on one of the N atoms of the amidine unit abolishes it A terminal aryl nucleus enhances activity but is not essential e g 3 bromo*cyclo*hexyl*iso*thiourea is as potent as phenyldiguanide Activity is also enhanced by the substitution of halogen or methyl into certain positions of the aryl nucleus Finally it may be noted that amidines are strong mono acidic bases and will exist at physiological *p*H s as cations (–C(NH_2)NH_2^+)

At this point it is convenient to mention some other vasodilator amidine derivatives which do not however contain an unsubstituted amidine unit

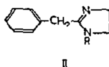
Hydralazine or 1 hydrazinophthalazine (I) belongs to a small group of phthalazine compounds which includes its 4-methyl 4-phenyl and 4-hydrazino derivatives all of comparable activity The integrity of the hydrazino group appears to be essential since its replacement by amino or substituted amino groups reduces activity drastically The mechanism of the hypotensive effect is obscure it develops gradually and is remarkably persistent (GROSS DRUEY and MEIER 1950)

It would be interesting to investigate the pharmacological properties of related compounds e g 2 hydrazino pyridine or quinoline and 1 or 3 hydrazino*iso*quinoline all of which would contain the amino amidine unit (N C NH NH_2)

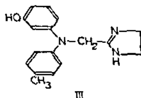
Hydralazine has some antiadrenaline action but much less anti noradrenaline action Tolazoline and phentolamine are more effective antagonists of adrenaline



I



II



III

mechanism of their hypotensive action which together with slowing of the heart and respiration, is produced reflexly by stimulation of afferent nerve endings in the heart and lungs (KRAYER and ACHESON, 1946), and in the fact that this reflex mechanism is not confined to the veratrum alkaloids but is displayed by what DAWES and COMROE (1954) have called a weird collection of chemical substances, such as adenosine triphosphate 5 hydroxytryptamine and certain amidines It would be as absurd to seek for structure action relation ships between such diverse substances as it would be to do so between saccharin and sucrose because they both taste sweet but the amidines at least do show some consistent relationships among themselves

Table 1 gives the names formulae, and activities of eight of the most active among some thirty to forty compounds of fairly simple structure, all containing one unsubstituted amidine group which DAWES and MOTT (1950) and DAWES and FASTIER (1950) found to

Table 1

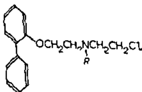
Vasodilator amidine derivatives

Name	Formula	Depressor activity*
Guanidines		
p-chlorophenylguanidine	4 Cl C_6H_4NH C(NH)NH_2	1·0
Diguanides		
phenyldiguanide	C_6H_5NH C(NH)NH C(NH)NH_2	1 0
o-chloro	2 Cl	2 5
p-chloro	4 Cl	1 5
o methyl	2 CH_3	1 5
Iso*thioureas*		
2 α naphthylethyl*iso*thiourea	α $C_{10}H_7CH_2CH_2S$ C(NH)NH_2	2 2
m-chlorobenzyl*iso*thiourea	3 $ClC_6H_4CH_2S$ C (NH)NH_2	1 1
cis 3 bromo*cyclo*hexyl*iso* thiourea	3 $BrC_6H_{10}S$ C(NH)NH_2	1 1

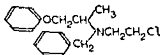
* In terms of phenyldiguanide

elicit a reflex fall in blood pressure and heart rate in the cat by an action on afferent nerve endings in the heart (the Bezold reflex) they also elicit a similar depressor reflex by an action on afferent endings in the lungs The approximate depressor potencies are given (Table 1) in terms of phenyldiguanide which is itself about 1/5th to 1/10th as active as pure veratridine All these amidines produce their depressor effects in doses of 1 mg/kg or less in the cat

that these compounds are preferentially adsorbed at the appropriate sites in virtue of the groups other than the β-chloroethyl group that intramolecular alkylation then occurs and that the ethylene immonium cation reacts with some nearby nucleophilic radical No other view seems to me to account for the specificity of these com pounds since the ethylene immonium cation if not tied down to particular sites would react readily with nucleophilic radicals at any situation This view is supported by the facts that the adrenaline block can be overcome in its early stage i e reversible adsorption at specific sites has already occurred and that blocking activity is enhanced by the presence in the drug molecule of an aryloxyethyl amine unit of structure which we know to confer competitive antiadrenaline properties—cf phenoxyethyldiethylamine (928F) and piperoxan (933F)—that is by exactly the unit of structure which would encourage adsorption of the molecule at the right sites Examples are the *o*-diphenyl ethers (V) of LOEW and MICETICH (1948 1949) in which maximum activity occurs when R is *n* amyl and the phenoxyethylchloroethylamines (NICKERSON and NOMAGUCHI 1951) of which dibenyline (VI) is the best known It is worth noting that phenoxyethylbenzylethylamines which lack the β-chloro group display reversible antiadrenaline properties



V R = alkyl



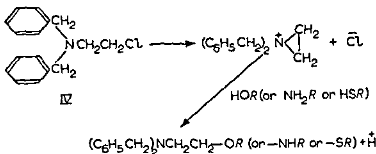
VI

Other essential structural features of this group of drugs are (*a*) a *tertiary* N atom sufficiently strongly basic to allow intramole cular alkylation to occur—hence the need to separate the aryl groups by one or more atoms from the N atom and (*b*) a β substituted ethyl group capable of alkylating the N atom a β halo or β sulphonyl group fulfils this condition

In recent years the alkaloids of *Rauwolfia* spp have attracted much attention Reserpine was isolated from *R serpentina* Benth in 1952 by MUELLER SCHLITTLER and BEIN its structure (VII) is closely related to that of yohimbine (DORFMAN *et al* 1954) Since 1952 several related alkaloids have been isolated e g deserpidine

Tolazoline (II R=H) is one of a group of iminazolines studied by Hartmann and Isler (1939) It produces peripheral vasodilatation and it blocks and even reverses the vasoconstrictor action of adrenaline It is an interesting compound because small changes in its structure convert it into a pressor agent e g its N methyl derivative (II $R=CH_3$) produces a rise of blood pressure by a nicotine like stimulation of sympathetic ganglia and the suprarenals (Gowdey 1948, 1949) This at first sight, remarkable reversal of properties may be due to an alteration in the balance of properties of tolazoline, its mild nicotine like effects being intensified at the expense of the vasodilator and antiadrenaline effects It would be interesting to know whether loading the iminazoline ring with alkyl groups larger than methyl would lead to ganglion blocking activity

Phentolamine (III) contains the *m* phenolic group so characteristic of the most potent sympathomimetic amines it has been variously estimated as from 5 to 10 times as active as tolazoline (Roberts Richardson, and Green 1952 Johnson Green and Lanier 1953) Both drugs block the effects of adrenaline or adrenergic stimulation competitively, and their effects are relatively transient



Dibenamine (IV) and its congeners on the other hand exert a noncompetitive antagonism to adrenaline and adrenergic stimulation Their effect develops slowly but after a latent period becomes relatively permanent during the latent period the effect can be overcome by excess adrenaline but not when the block has become well established The generally accepted view is that these compounds are first converted to ethylene immonium ions which then react with nucleophilic groups (possibly hydroxyl amino or sulphydryl groups) to form stable covalent derivatives of tissue constituents this view is supported by kinetic studies of the hydrolysis of dibenamine in aqueous solution (Harvey and Nickerson 1953) My own view is

ester of methyl reserpate*, also the distribution of reserpine containing C^{14} in the carboxyl group of trimethoxybenzoic acid since methyl reserpate itself is inactive

We must now turn to ganglion blocking agents some of which have been widely used in recent years in the treatment of hypertension It will be useful to glance first at the types of bases which

Table 2

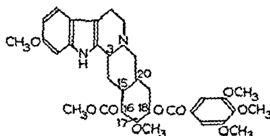
Ganglionic Stimulators

Type of base	Example
Secondary	Cytisine Nornicotine
Tertiary	Nicotine Lobeline N methylcytisine (caulophylline)
Mono-onium salts	Choline esters and ethers e g acetylcholine phenyl ether of choline etc Aryl and arylalkyl trimethylammonium salts e g phenyltrimethylammonium, hordenine methiodide etc Tetra alkylammonium salts of types (1) $R\overset{+}{N}Me_3$ e g $\overset{+}{N}Me_4$ etc (2) $R_2\overset{+}{N}Me_2$ e g $Et_2\overset{+}{N}Me_2$ and dimethyl phenyl piperazinium (DMPP) trimethylsulphonium, $Me_3\overset{+}{S}$
Bis-onium salts	Choline ester of propionic betaine $Me_3\overset{+}{N}CH_2CH_2OCOCH_2CH_2\overset{+}{N}Me_3$

stimulate ganglia (Table 2) and note that they include secondary and tertiary bases as well as mono and bis-onium salts Most ganglion stimulators also block transmission in ganglia when administered in large doses this is true not only of onium salts but also of secondary and tertiary bases like cytisine and nicotine consequently ganglionic blocking activity is not confined to quaternary bases—this is the first point to note The second is that nearly all quaternary bases which stimulate ganglia have three methyl groups attached to the onium atom (N or S) A few quaternary salts carrying two methyl groups on the N atom are known to stimulate ganglia e g dimethyldiethylammonium (WIEN MASON EDGE and LANGSTON 1952) and dimethylphenylpiperazinium

* This ester has been described in Brit. Pat. 744 290 (1954)

from *R canescens* (SCHLITTLER *et al*, 1955) which lacks the methoxyl in the indole nucleus of reserpine, and rescinnamine (KLOHS, DRAPER and KELLER, 1954) which has a 3 4 5 trimethoxycinnamoyl group in place of the trimethoxybenzoyl group of reserpine



VII

Reserpine has six asymmetric C atoms (3 15 16 17 18 and 20) and therefore a considerable number of stereoisomers are possible This fact may make its synthesis difficult Considerable progress has already been made in elucidating the relative configurations around the asymmetr c centres

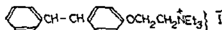
The main interest of reserpine at present lies in unravelling its pharmacology and evaluating its clinical usefulness More questions can be asked than answered about its structure action relationships The onset of its effects is relatively slow even after parenteral administration, and consequently there is a possibility that some at least, of its effects may be due to a metabolite of it We know that the methoxyl in the indole nucleus is not essential since deserpidine does not differ significantly in its effects from reserpine (SCHNEIDER *et al* 1955) The integrity of the trimethoxybenzoyl group is presumably important since its replacement by other acyl groups (veratroyl anisoyl benzoyl furoyl nicotinyl phenylacetyl acetyl etc) lowers activity and lowers its progressively the more the acyl group differs in structure from trimethoxybenzoyl (SCHLITTLER *et al* 1954)

SHEPPARD LUCAS and TSEIN (1955) made the curious observation that when reserpine labelled with C^{14} in the 4 methoxy group of the acyl residue was fed to rats no radioactive carbon could be detected in the brain Since 24 per cent of the C^{14} was excreted as expired $C^{14}O_2$ they postulated oxidative demethylation It might be instructive to investigate the 3 5 dimethoxy-4 hydroxybenzoic (syringic)

triethylsulphonium and the thiophanium compound arfonad (anion = (+) camphor sulphonate) I do not know of any exception to this rule

I should like to go further and suggest a second rule viz that the more powerful a stimulator the methylated onium salt is the more powerful a blocking agent the analogous ethylated onium salt will be This second rule is put forward as a working hypothesis but I can give one example of it the *m* bromophenyl ether of choline is about 3 5 times as powerful a nicotine like pressor agent as choline phenyl ether (HEY 1952) similarly *m* bromophenoxyethyl triethylammonium is about 3 times as potent an inhibitor of the superior cervical ganglion (cat) as phenoxyethyltriethylammonium (2512F) and about 4 times as powerful a depressor agent (unpublished results) Since 2512F is about 10 times as potent a ganglionic blocker as tetraethylammonium (BULBRING and DEPIERRE 1949) its *m* bromo derivative must be 30–40 times as potent i e about as potent as hexamethonium

From HEY s work we already know at least one factor which increases the stimulant nicotine like activity of choline ethers viz. the presence of a terminal group which increases the mesomeric deviation towards structures of the type $\bar{R}-\overset{+}{O}-CH_2CH_2\overset{+}{N}Me_3$ My tentative second rule suggests that a similar increase in blocking potency will occur in ethers of the type $R-O-CH_2CH_2\overset{+}{N}Et_3$ In this connection Elvetil (VIII) is interesting because the stilbene residue should be more eff ctive than the phenyl group in causing the mesomeric deviation HEY envisages (CAVALLINI *et al* 1953)



VIII

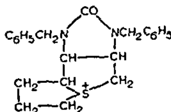
The thiophanium compound Arfonad or trimethaphan (RANDALL PETERSON and LEHMANN 1949) calls for a few remarks It is about 30 times as potent as tetraethylammonium It will be noticed that the S atom is loaded with heavier radicals than ethyl the potency depends upon this loading because loss of one or both benzyl radicals decreases it drastically Also the cation is stereo specific since arfonad which is the (+)-camphor sulphonate of the *dextro* rotatory base is about twice as active as the salt of the *laevo* base The hypotensive effect of arfonad is complex in large doses it

(DMPP) (CHEN, PORTMANN and WICKEL 1951) but I do not know of any quaternary salt with less than two N methyl groups which stimulates ganglia The third point is that bis trimethylammonium salts are not inevitably ganglion blocking agents since the last compound in the Table is a powerful ganglionic stimulator

If we now look at mono onium salts which have a purely blocking action on ganglia (Table 3) we shall notice that they all contain

Table 3

Mono onium salts

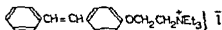
Ganglionic stimulators	Ganglion blocking agents
Acetylcholine $CH_3CO_2CH_2CH_2\overset{+}{N}Me_3$	*Acetoxyethyltriethylammonium* $CH_3CO_2CH_2CH_2\overset{+}{N}Et_3$
Tetramethylammonium $Me_4\overset{+}{N}$	Tetra ethylammonium $Et_4\overset{+}{N}$ Diethyl di *iso*propylammonium $Et_2\overset{+}{N}isoPr_2$
Choline phenyl ether $C_6H_5OCH_2CH_2\overset{+}{N}Me_3$	*Phenoxyethyltriethylammonium* (2512F) $C_6H_5OCH_2CH_2\overset{+}{N}Et_3$
Choline *n* bromophenyl ether 3 $BrC_6H_4OCH_2CH_2\overset{+}{N}Me_3$	*m* Bromophenoxyethyltriethyl ammonium 3 $BrC_6H_4OCH_2CH_2\overset{+}{N}Et_3$
Trimethylsulphonium $Me_3\overset{+}{S}$	Triethylsulphonium $Et_3\overset{+}{S}$
	Arfonad (*d*-camphor sulphonate) 

groups larger than methyl on the onium atom These and many other examples lead me to suggest the rule that in any ganglionic stimulator which contains *one* methylated onium atom replacement of all the methyl groups by heavier groups will convert the com pound into a purely blocking agent This is true not only of quaternary ammonium salts but also of sulphonium salts e g

triethylsulphonium and the thiophanium compound arfonad (anion = (+) camphor sulphonate) I do not know of any exception to this rule

I should like to go further and suggest a second rule viz that the more powerful a stimulator the methylated onium salt is the more powerful a blocking agent the analogous ethylated onium salt will be This second rule is put forward as a working hypothesis but I can give one example of it the *m* bromophenyl ether of choline is about 3 5 times as powerful a nicotine like pressor agent as choline phenyl ether (HEY 1952) similarly *m* bromophenoxyethyl triethylammonium is about 3 times as potent an inhibitor of the superior cervical ganglion (cat) as phenoxyethyltriethylammonium (2512F) and about 4 times as powerful a depressor agent (unpublished results) Since 2512F is about 10 times as potent a ganglionic blocker as tetraethylammonium (BULBRING and DEPIERRE 1949) its *m* bromo derivative must be 30–40 times as potent i e about as potent as hexamethonium

From HEY s work we already know at least one factor which increases the stimulant nicotine like activity of *choline ethers* viz. the presence of a terminal group which increases the *mesomeric* deviation towards structures of the type $\bar{R}-\bar{O}-CH_2CH_2\overset{+}{N}Me_3$ My tentative second rule suggests that a similar increase in blocking potency will occur in ethers of the type $R{-}O{-}CH_2CH_2\overset{+}{N}Et_3$ In this connection Elvetil (VIII) is interesting because the stilbene residue should be more effective than the phenyl group in causing the mesomeric deviation HEY envisages (CAVALLINI *et al* 1953)



VIII

The thiophanium compound Arfonad or trimethaphan (RANDALL PETERSON and LEHMANN 1949) calls for a few remarks It is about 30 times as potent as tetraethylammonium It will be noticed that the S atom is loaded with heavier radicals than ethyl the potency depends upon this loading because loss of one or both benzyl radicals decreases it drastically Also the cation is stereospecific since arfonad, which is the (+)-camphor sulphonate of the *dextro*-rotatory base is about twice as active as the salt of the *laevo* base The hypotensive effect of arfonad is complex in large doses it

liberates histamine but when the effect of released histamine is annulled by an antihistamine and the ganglionic effect is eliminated by anatomical means the drug still produces a fall of blood pressure (dog) this residual hypotensive effect is attributed to a direct vasodilator action (McCubbin and Page, 1952)

I can find no simple rules governing the structure action relationships of bis onium ganglionic blocking agents The ganglion stimulant action of the choline ester of propionic betaine ($Me_3\overset{+}{N}CH_2CH_2OCOCH_2CH_2\overset{+}{N}Me_3$) rules out the simple view that two NMe_3 groups linked by a six atom chain will confer purely blocking activity This betaine ester has some muscarinic activity, but whereas the nicotinic properties of acetylcholine on blood pressure are only clearly manifested after atropine the muscarinic properties of this betaine ester are only fully revealed after tetra ethylammonium (Schueler, Keasling 1951) When the six methyl groups are all replaced by ethyl, purely blocking activity on ganglia is observed, but this effect can also be achieved by replacing the ester unit (–O CO–) by two methylene groups ($-CH_2CH_2-$) so that *one might say that the blocking action of hexamethonium is due to* this replacement It would be instructive to study the pharmacology of the compounds in which either the ether O atom or the carbonyl unit of the ester group was replaced by methylene

Table 4

Bis onium Salts symmetrical with respect to endgroups

Type of chain	*n*	Endgroups in order of decreasing activity on sympathetic ganglia
(1) $-(CH_2)-$	4	$NMeEt_2 \gg NMe_2Et > NEt_3 > NMe_3$
	5	$NMe_2Et > NMeEt_2 > NMe_3 > NEt_3$
	6	$NMe_2Et > NMe_3 > NMeEt_2 \gtrsim NEt_3$
	7	$NMeEt_2 > NMe_3 \bumpeq NMe_2Et > NEt_3$
(2) $-(CH_2)NMe(CH_2)-$	2	$NMe_2Et > NMe_3 \gg NEt_3$
(3) $-C_6H_4-(CH_2)_n-$	2	$NMe_2Et > NMe_3 > NMeEt_2 \gg NEt_3$
	3	$NMe_3 > NMe_2Et > NMeEt_2 > NEt_3$
	4	$NMe_2Et > NMeEt_2 > NMe_3 > NEt_3$

The sign $\gg$ means 10 times as active or more

(1) Wien Mason Edge and Langston (1952)
(2) Bein and Meier (1950)
(3) Wien and Mason (1953)

The potencies of bis-onium salts depend both on the chain length and on the nature of the endgroups The chain length can vary from 4 to 7 atoms but the most effective endgroup varies with the length of the chain (Table 4) For a 5 atom chain the most effective trialkylammonium group (so far as we know) is NMe_2Et but it might be worth while trying other endgroups e g NMe_2isoPr Chains of more or less than 5 atoms show no consistency For most chain lengths NEt_3 is the least effective endgroup

A somewhat clearer picture is obtained by considering the influence of chain length on the effectiveness of a given endgroup (Table 5) It will be seen that for all endgroups except NMe_3 a

Table 5

Symmetrical polymethylene bis onium salts $R_3\overset{+}{N}-(CH_2)-\overset{+}{N}R_3$

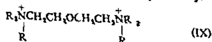
Endgroup	Chain lengths in order of decreasing activity on sympathetic ganglia
NMe_3	6 > 5 > 7 > 4
NMe_2Et	6 = 5 > 7 = 4
$NMeEt_2$	5 > 4 > 6 > 7
NEt_3	5 > 4 > 6 > 7
NMe	5 > 6 > 4 ≫ 3
NMe	5 ≃ 6 = 4 > 7 ≫ 3
O NMe	5 = 6 > 7 > 4

WIEN *et al* (1952) MASON and WIEN (1955)

pentamethylene chain gives maximum activity but again there is no consistent relationship for other chain lengths The 1 methyl pyrrolidine endgroup is the most effective of all those listed in Table 5

So far all the bis-onium salts considered have been symmetrical with respect to their endgroups Recently some interesting new types of bis onium salts unsymmetrical with respect to their endgroups have been announced

FAKSTORP and PEDERSEN (1954) studied bis onium salts of the type (IX) where R R and R were methyl or ethyl

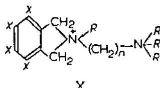


$$R_2\overset{+}{N}CH_2CH_2OCH_2CH_2\overset{+}{N}R_2 \qquad \text{(IX)}$$

and found that blocking activity for both sympathetic and para sympathetic ganglia was greatest when R was methyl and R and

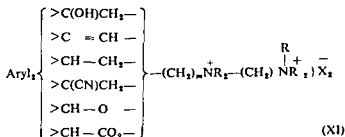
R″ were ethyl groups, i e in the unsymmetrical cation $Me_2Et\overset{+}{N}CH_2CH_2OCH_2CH_2\overset{+}{N}Et_3$ This cation was much more active than the symmetrical cations containing two Me_3N or Et_3N groups, and about 3–5 times as active as the symmetrical cation containing two Me_2EtN groups Less pronounced differences were observed among the analogous thio ethers but again the compound containing one Me_2EtN and one Et_3N as endgroups had the highest activity

A second example of the unsymmetrical bis onium salts is provided by *iso*indoline compounds of the general formula (X)



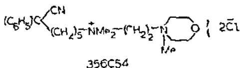
In these compounds the intensity and duration of blocking action appear to depend upon the value of n the nature of R and R and of substituents in the benzene ring Maximum duration and potency occurs when $n = 2$ R = R = CH_3 and X is chlorine the compound fulfilling these conditions—chlor*iso*indoline or ecolid —is said to be well absorbed after oral administration its ganglionic blocking effect is rapid in onset and very prolonged The ready absorption from the gastrointestinal tract and the prolonged action appear to depend upon chlorination of the benzene ring they do not occur in tetrabromo compounds (Plummer Trapold Schneider, Maxwell and Earl 1955)

Adamson Billinghurst and Green (1956) have recently announced a new series of unsymmetrical bisonium salts of the general type (XI)



The compounds are derived from a series of spasmolytics analgesics and antihistamines containing one tertiary or quaternary

N atom (left of dotted line) previously described by the Wellcome Research Unit at Beckenham the addition of a second quaternary N atom attached to the tertiary or quaternary N atom by a short polymethylene chain confers ganglion blocking activity and abolishes the previous types of activity Activity is favoured by the following features $n = 2$ or 3 $m = 3$ or 4 $R = CH_3$ or C_2H_5 and NR_2 is a cyclic structure The most promising compound appears to be 356C54



356C54

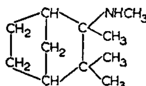
Like most bisonium salts these compounds are poorly absorbed after oral administration (10 times S C dose required) but after subcutaneous injection they have a prolonged effect (7 to 12 hours)

In conclusion I should like to make two general comments on ganglion blocking agents as drugs for the treatment of hypertension

(i) There is no doubt that many onium salts particularly bis quaternary ammonium salts are extremely effective hypotensive drugs when administered parenterally Their disadvantage is that they are poorly or irregularly absorbed after oral administration Absorption varies with the nature of the endgroups e g pentolinium appears to be absorbed better than hexamethonium and possibly attachment of a strongly lipophilic group to one N atom as in chlorisondoline may assist absorption Absorption also appears to depend upon the anion (HARINGTON 1953) which is strange and difficult to understand However what we can say with certainty is that tertiary or bistertiary bases would be absorbed much more readily than quaternary or bisquaternary salts and I should like to suggest that the most promising field for future research in this field is the study of tertiary or bistertiary bases as ganglionic blocking agents I have already pointed out that both secondary and tertiary bases are known which stimulate ganglion cells in small doses and block them in large doses There is therefore no reason to assume that purely blocking agents cannot be found among secondary and tertiary bases I will mention three nonquaternary bases which have purely blocking activity

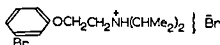
Inversine or mecamylamine (XII) is a secondary base (3 methyl aminoisocamphane)

hexamethonium to be as *effective after oral as after parenteral* administration and to have a slow onset and a prolonged action (Moyer Dennis and Ford 1956 Stone Torchiana O Neill and Beyer 1956)



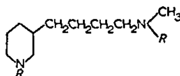
XII

m Bromophenoxyethyldi *iso*propylamine hydrobromide (XIII) has been tested on the superior cervical ganglion of the cat It is about 2/5th as active a blocking agent as phenoxyethyltriethyl ammonium (2512F) i e about four times as active as tetraethyl ammonium It has as might be expected mild antiadrenaline properties in the spinal cat It was investigated as a direct result of the two rules which I mentioned earlier (unpublished results)



XIII

3 (δ Dimethylaminobutyl) 1 methylpiperidine (XIV $R = CH_3$) was reported by Phillips (1954) to be at least as active as hexa methonium intravenously and much more effective after oral administration The disecondary base (XIV R=H) was also active but less so than the ditertiary base The dimethiodide of the ditertiary base was more active but had a less favourable toxicity activity ratio than the ditertiary base I have not seen a full report of the pharmacology of these compounds It will be noticed that the nitrogen atoms are separated by a six carbon chain



XIV

These three types of bases at least demonstrate that nonquaternary blocking agents can be found

On purely chemical grounds I should expect nonquaternary blocking agents to be reliably and almost completely absorbed after oral administration They would probably be less active than their quaternary salts but reliable absorption might easily outweigh lower activity and we have a factor of about ten to play with here I should also expect them to have a more prolonged effect since secondary and tertiary bases are usually more firmly adsorbed at surfaces than quaternary salts A possible disadvantage of nonquaternary bases is that they might have a less highly specific effect so that only nonquaternary bases with high blocking activity would be likely to be of clinical use

(ii) The second general comment is that a systematic investigation is needed of the relative activities of ganglion blocking agents on sympathetic and parasympathetic ganglia Examples are already known of blocking agents which discriminate between sympathetic and parasympathetic ganglia e g Elvetil is reported to be relatively more effective at parasympathetic than at sympathetic ganglia (CAVALLINI *et al* 1953) and the reverse is true of tetramethylene bis-diethylmethylammonium (WIEN *et al* 1952) PERRY and WILSON (1956) have pointed out that comparison of blocking activities on sympathetic and parasympathetic ganglia must be made in the same species and preferably on the same endorgan concurrently Using presynaptic stimulation of the thoracic sympathetic chain and of the vagus to the cat heart they found that pentamethonium was 10 times as effective in blocking the parasympathetic as in blocking the sympathetic ganglia whereas hexamethonium and azamethonium showed no selective blocking action The use of this or similar methods may enable us to discover what structural features favour preferential block of sympathetic ganglia

REFERENCES

ADAMSON D W BILLINGHURST J W and GREEN A F (1956) *Nature* 177 523
BEIN H J and MEIER R (1950) *Experientia* 6 351
BEZOLD A VON and HIRT L (1867) *Unters physiol Lab Wurzburg* 1 75
BULBRING E and DEPIERRE F (1949) *Brit J Pharmacol* 4 22
CAVALLINI G MANTEGAZZA P MASSARINI E and TOMMASSINI R (1953) *Il Farmaco* (Pavia) *Ed Sci* 8 317
CHEN G PORTMAN R and WICKEL A (1951) *J Pharmacol* 103 330
DAWES G S and COMROE JR J H (1954) *Physiol Rev* 34 167
DAWES G S and FASTIER F N (1950) *Brit J Pharmacol* 5 65
DAWES G S and MOTT J C (1950) *Brit J Pharmacol* 5 323
DORFMAN L FURLENMEIER A HEUBER C F LUCAS R MACPHILLAMY H B MUELLER J M SCHLITTLER E SCHWYZER R and ANDRE A F ST (1954) *Hel Chim Acta* 37 59
FAKSTORP J and PEDERSEN J G A (1954) *Acta pharmacol et toxicol* 10 7

Gowdey C W (1948) *Brit J Pharmacol* 3 254
Gowdey C W (1949) *Brit J Pharmacol* 4 45
Gross F Druey J and Meier R (1950) *Experientia* 6, 19
Harington M (1953) *Clin Sci* 12 185
Hartmann M and Isler H (1939) *Arch exp Path Pharmak* 192 141
Harvey S C and Nickerson M (1953) *J Pharmacol* 109 328
Hey P (1952) *Brit J Pharmacol* 7 117
Johnson H D Green H D and Lanier J T (1953) *J Pharmacol* 108 144
Klohs M W Draper M D and Keller F (1954) *J Amer Chem Soc* 76 2843
Krayer O and Acheson G H (1946) *Physiol Rev* 26 383
Loew E R and Micetich A (1948) *J Pharmacol* 93 434
Loew E R and Micetich A (1949) *J Pharmacol* 95 448
Mason D F J and Wien R (1955) *Brit J Pharmacol* 10 124
McCubbin J W and Page I H (1952) *J Pharmacol* 105 437
Moyer J H Dennis E and Ford R (1956) *J Pharmacol* 116 44
Mueller J M Schlittler E and Bein H J (1952) *Experientia* 8 667
Nickerson M and Nomaguchi G (1951) *J Pharmacol* 101 379
Perry W L M and Wilson C W M (1956) *Brit J Pharmacol* 11 81
Phillips A P (1954) *J Amer Chem Soc* 76 2211
Plummer A J Trapold J H Schneider J S Maxwell R A and Earl A E (1955) *J Pharmacol* 115 172
Randall L O Peterson W G and Lehmann G (1949) *J Pharmacol* 97 48
Roberts G Richardson A W and Green H D (1952) *J Pharmacol* 105 466
Schlittler E MacPhillamy H B Dorfman L Furlenmeier A Helbner C F Lucas R Mueller J M Schwyzer R and André A F St (1954) *Ann N Y Acad Sci* 59 1
Schlittler E Ulshafer P Pandow M L Hunt R and Dorfman L (1955) *Experientia* 11 64
Schneider J A Plummer A J Earl A E Barrett W E Rinehart R and Dibble R C (1955) *J Pharmacol* 114 10
Schueler F W and Keasling H H (1951) *J Pharmacol* 103 222
Sheppard H Lucas R C and Tsien W H (1955) *Arch int Pharmacodyn* 103 256
Stone C A Torchiana M L O'Neill G Q and Beyer K H (1956) *J Pharmacol* 116 54
Wien R and Mason D F J (1953) *Brit J Pharmacol* 8 306
Wien R Mason D F J Edge N D and Langston G T (1952) *Brit J Pharmacol* 7 534
Zaimis E J (1955) *J Pharm Pharmacol* 7 497

BIOCHEMICAL PRINCIPLES IN RELATION TO HYPOTENSIVE DRUG ACTION

H BLASCHKO

THE biochemist s ideas on the contribution of the nervous system to the regulation of arterial blood pressure are determined by the new knowledge of the chemical activities of the nervous system The blood pressure like all visceral functions is regulated by the release of a number of substances which excite (or inhibit) effector cells The effectors are either muscle plain and cardiac or nerve cells in the central nervous system and in autonomic ganglia

The effector cells carry on their surface the so-called receptors these are structures possibly proteins that react specifically with the active substances released by nerve endings or secreting cells The reaction between an active substance *A* and the specific receptor is a reversible one it can be described thus



(1) A + Receptor $\rightleftharpoons$ A Receptor $\longrightarrow$ Response $\longrightarrow$

The *A* receptor complex determines the response of the excitable tissue Reversibility of the reaction must be assumed in order to account for the short refractory periods and the ensuing readiness of the receptors to react again with *A* Although the presentation of the reaction between *A* and the receptor as given above may be an oversimplification—this will be discussed below—we may say that the reversibility of reaction (1) implies that the law of mass action holds and that the response i e the number of receptors combined with *A* depends upon the *concentration of uncombined substance A in the neighbourhood of the receptors*

An enquiry into the factors governing the response of the excitable tissue to nerve stimulation will thus resolve itself into

(a) *the study of the reaction between active substance A and the receptor* and

Gowdey C W (1948) *Brit J Pharmacol* 3 254
Gowdey C W (1949) *Brit J Pharmacol* 4 45
Gross F Drury J and Meier R (1950) *Experientia* 6, 19
Harington M (1953) *Clin Sci* 12 185
Hartmann M and Isler H (1939) *Arch exp Path Pharmak* 192, 141
Harvey S C and Nickerson M (1953) *J Pharmacol* 109 328
Hey P (1952) *Brit J Pharmacol* 7 117
Johnson H D Green H D and Lanier J T (1953) *J Pharmacol* 108 144
Klohs M W Draper M D and Keller F (1954) *J Amer Chem Soc* 76 2843
Krayer O and Acheson G H (1946) *Physiol Rev* 26 383
Loew E R and Micetich A (1948) *J Pharmacol* 93 434
Loew E R and Micetich A (1949) *J Pharmacol* 95 448
Mason D F J and Wien R (1955) *Brit J Pharmacol* 10 124
McCubbin J W and Page I H (1952) *J Pharmacol* 105 437
Moyer J H Dennis E and Ford R (1956) *J Pharmacol* 116 44
Mueller J M Schlittler E and Bein H J (1952) *Experientia* 8 667
Nickerson M and Nomaguchi G (1951) *J Pharmacol* 101 379
Perry W L M and Wilson C W M (1956) *Brit J Pharmacol* 11 81
Phillips A P (1954) *J Amer Chem Soc* 76 2211
Plummer A J Trapold J H Schneider J S Maxwell R A and Earl A E (1955) *J Pharmacol* 115 172
Randall L O Peterson W G and Lehmann G (1949) *J Pharmacol* 97 48
Roberts G Richardson A W and Green H D (1952) *J Pharmacol* 105 466
Schlittler E Macphillamy H B Dorfman L Furlenmeier A Heubner C F Lucas R Mueller J M Schwyzer R and André A F St (1954) *Ann N Y Acad Sci* 59 1
Schlittler E Ulshafer P Pandow M L Hunt R and Dorfman L (1955) *Experientia* 11 64
Schneider J A Plummer A J Earl A E Barrett W E Rinehart R and Dibble R C (1955) *J Pharmacol* 114 10
Schueler F W and Keasling H H (1951) *J Pharmacol* 103 222
Sheppard H Lucas R C and Tsien W H (1955) *Arch int Pharmacodyn* 103, 256
Stone C A Torchiana M L O'Neill G Q and Beyer K H (1956) *J Pharmacol* 116 54
Wien R and Mason D F J (1953) *Brit J Pharmacol* 8 306
Wien R Mason D F J Edge N D and Langston G T (1952) *Brit J Pharmacol* 7 534
Zaimis E J (1955) *J Pharm Pharmacol* 7 497

BIOCHEMICAL PRINCIPLES IN RELATION TO HYPOTENSIVE DRUG ACTION

H BLASCHKO

The biochemist s ideas on the contribution of the nervous system to the regulation of arterial blood pressure are determined by the new knowledge of the chemical activities of the nervous system The blood pressure like all visceral functions is regulated by the release of a number of substances which excite (or inhibit) effector cells The effectors are either muscle plain and cardiac or nerve cells in the central nervous system and in autonomic ganglia

The effector cells carry on their surface the so-called receptors these are structures possibly proteins that react specifically with the active substances released by nerve endings or secreting cells The reaction between an active substance A and the specific receptor is a reversible one it can be described thus



(1) A + Receptor $\rightleftharpoons$ A Receptor > Response >

The A receptor complex determines the response of the excitable tissue Reversibility of the reaction must be assumed in order to account for the short refractory periods and the ensuing readiness of the receptors to react again with A Although the presentation of the reaction between A and the receptor as given above may be an oversimplification—this will be discussed below—we may say that the reversibility of reaction (1) implies that the law of mass action holds and that the response i e the number of receptors combined with A depends upon the *concentration of uncombined substance A in the neighbourhood of the receptors*

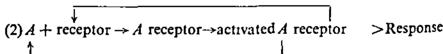
An enquiry into the factors governing the response of the excitable tissue to nerve stimulation will thus resolve itself into

(a) *the study of the reaction between active substance A and the receptor* and

(b) *the study of the factors that modify the concentration of uncombined substance A in the neighbourhood of the receptors*

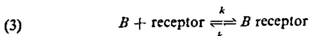
For the understanding of drug action, it is important to remember that chemical specificities are involved at both stages An effect by drugs on the response of the excitable tissue can be achieved either by an interference with the reaction between *A* and the receptor (and with the subsequent events in the effector itself) or by an alteration of the concentration of uncombined active substance *A* From what has been said it is clear that drugs acting upon the reaction between *A* and receptor are more directly linked with the response of the excitable cell, in the management of a chronic disorder, however, a more distant site of attack may not be a disadvantage

It should be added that equation (1) may be too simplified a representation of the reaction between *A* and the receptor The complex *A* receptor may not determine the response directly, it may first be altered and it may be this altered activated , *A* receptor complex that elicits the response of the effector Thus the complex that releases *A* may not be the same chemical entity that originally combined with *A* This would lead to a modification of equation (1)


(2) A + receptor → A receptor → activated A receptor >Response

However such a modification of equation (1) would not materially affect the arguments in the present state of our knowledge of the drug receptor reaction

Interference with the reaction between active substance and receptor is brought about by the competitive blocking agents these substances act by reducing the number of receptors free to combine with *A* For the reaction between a competitive blocking agent *B* and a receptor a true reversibility can be assumed the reaction can be formulated thus

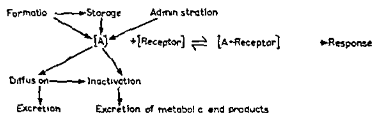


$$(3) \qquad B + \text{receptor} \underset{k}{\overset{k}{\rightleftharpoons}} B \text{ receptor}$$

The relation between receptor naturally occurring active substance and blocking agent can thus be compared to that between

haemoglobin oxygen and carbon monoxide This relationship is governed by the velocity constants of the reactions of association and dissociation It is worth while to keep this relationship in mind From the point of view of therapeutic usefulness the study of the dissociation constant of the drug *B* receptor complex k_2 is of particular interest as it is this constant that determines the decay of the *B* receptor complex and thus the duration of the blocking action for the treatment of a chronic disease a long lifetime of the drug receptor complex is of particular importance To the bio chemist pharmacological methods for the separate determination of constants k_1 and k_2 seem therefore desirable

In the following an attempt is made to define some of the factors *that determine* the concentration of uncombined active substance *A* in the neighbourhood of the receptors These factors are diagram matically shown below



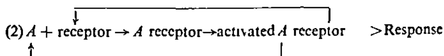
Th diagram shows three factors which increase the concentration of uncombined active substance in the neighbourhood of the receptors formation release from storage and administration for reasons of therapy or experiment The factors that decrease the concentration of active substance are diffusion and inactivation by enzymes A horizontal arrow is drawn between formation and storage this is to indicate that formation of new active substance does not usually increase the concentration of free active substance in the neighbourhood of the receptors directly but that usually the newly formed material is stored and then released from storage either from nerves or from secreting cells (including mast cells) In this respect there appears to exist a striking similarity between the function of secretory and nerve cells

A horizontal arrow is also drawn between diffusion and inactivation in order to remind us that in many instances diffusion away from the receptors precedes *inactivation*

(b) *the study of the factors that modify the concentration of uncom bined substance A in the neighbourhood of the receptors*

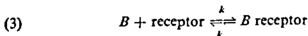
For the understanding of drug action, it is important to remember that chemical specificities are involved at both stages An effect by drugs on the response of the excitable tissue can be achieved either by an interference with the reaction between *A* and the receptor (and with the subsequent events in the effector itself) or by an alteration of the concentration of uncombined active substance *A* From what has been said it is clear that drugs acting upon the reaction between *A* and receptor are more directly linked with the response of the excitable cell, in the management of a chronic disorder, however, a more distant site of attack may not be a disadvant age

It should be added that equation (1) may be too simplified a representation of the reaction between *A* and the receptor The complex *A* receptor may not determine the response directly, it may first be altered, and it may be this altered, activated , *A* receptor complex that elicits the response of the effector Thus the complex that releases *A* may not be the same chemical entity that originally combined with *A* This would lead to a modification of equation (1)

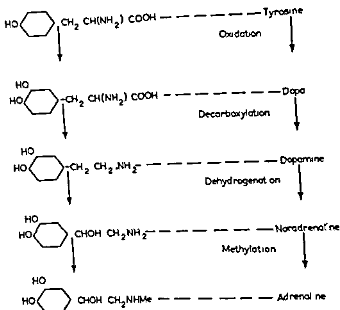


However such a modification of equation (1) would not materially affect the arguments in the present state of our knowledge of the drug receptor reaction

Interference with the reaction between active substance and receptor is brought about by the competitive blocking agents these substances act by reducing the number of receptors free to combine with *A* For the reaction between a competitive blocking agent *B* and a receptor a true reversibility can be assumed the reaction can be formulated thus



The relation between receptor naturally occurring active sub stance and blocking agent can thus be compared to that between



The formation of dopamine from dopa is the step catalysed by the decarboxylase

This scheme remained without supporting evidence until my colleague Dr H LANGEMANN (1950 1951) showed that large amounts of dopa decarboxylase occurred in chromaffin tissue He found the enzyme in the bovine adrenal medulla his observation has been confirmed (SOURKES HENEAGE and TRANO 1952) and the enzyme has since been demonstrated in the medulla of a number of other species including the rhesus monkey (D IORIO unpublished) and the chicken (HAGEN unpublished)

LANGEMANN S observation demonstrated for the first time the high amine forming ability of the chromaffin tissue It is of interest to note that dopa decarboxylase has recently also been found in the nervous system and particularly in sympathetic ganglia and nerves (HOLTZ and WESTERMANN 1956) Further support for the scheme comes from the finding of dopamine in human urine (HOLTZ CREDNER and KRONENBERG 1947 EULER HAMBERG and HELLNER 1951 WEIL MALHERBE 1956) in chromaffin tissue (GOODALL 1951 SHEPHERD and WEST 1953) and in sympathetic nerves (SCHUMANN 1956)

The diagram given is incomplete in many ways, it neglects entirely the link between the *A* receptor complex and the response of the effector cell, it also does not take into account permeability barriers and the possibility that in the transport of active substances across cell membranes specific factors may take a part For the pressor amines, this possibility has been more fully discussed elsewhere (BLASCHKO 1954) However, no certain examples of drug action by interference with passage of pressor amines through membranes are known at present

Interference by drug action with the concentration of free active substance can be achieved by acting upon one of three factors shown in the diagram these are formation storage and inactivation Both formation and inactivation depend upon the presence of enzymes and these enzymes can be inhibited Storage of active material depends upon specific storage mechanisms probably nonenzymic and interference with these storage mechanisms by drugs may cause release of active substance

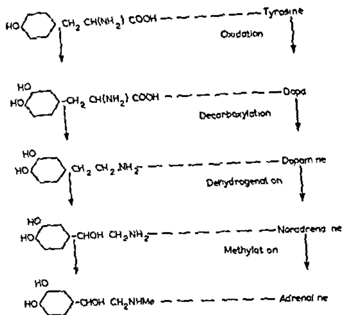
In the following some observations will be discussed which show that specific factors are involved in biosynthesis release and inactivation of active substance The examples given may at first sight appear far removed from therapeutic considerations but they have been chosen because the active substances referred to are known to affect the arterial blood pressure

I BIOSYNTHESIS OF PRESSOR AMINES

Interference with the arterial blood pressure might be achieved by inhibiting the formation of the pressor amines adrenaline and noradrenaline

In 1939 a scheme of biosynthesis was put forward (BLASCHKO 1939) which was based on a study of the enzyme dopa decarboxylase described by HOLTZ HEISE and LUDTKE (1938) It was found that this enzyme was unable to decarboxylate N methylated amino acids e g N methyl dopa this led to the suggestion that the formation of a primary amine preceded the formation of adrenaline The discovery of noradrenaline has made this part of the scheme extremely probable (see BÜLBRING 1949)

The sequence of reactions which leads to adrenaline takes as its starting point the amino acid tyrosine which is present in many proteins taken in with our food The sequence proposed is the following



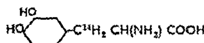
The formation of dopamine from dopa is the *step catalysed* by the decarboxylase

This scheme remained without supporting evidence until my colleague Dr H LANGEMANN (1950 1951) showed that large amounts of dopa decarboxylase occurred in chromaffin tissue He found the *enzym* in the bovine *adrenal* medulla his observation has been confirmed (SOURKES HENEAGE and TRANO 1952) and the enzyme has since been demonstrated in the medulla of a number of other species including the *rhe us monkey* (D IORIO unpublished) and the chicken (HAGEN unpublished)

LANGEMANN S observation demonstrated *for* the first time the high amine forming ability *of* the chromaffin tissue It is of interest to note that dopa decarboxylase has recently also been found in the nervous system and particularly in sympathetic ganglia and nerves (HOLTZ and WESTERMANN 1956) Further support for the scheme comes from the finding of dopamine in human urine (HOLTZ CREDNER and KRONENBERG 1947 EULER HAMBERG and HELLNER 1951 WEIL MALHERBE 1956) in chromaffin tissue (GOODALL 1951 SHEPHERD and WEST 1953) and in sympathetic nerves

The scheme of biosynthesis of noradrenaline and adrenaline outlined above, has not found general acceptance EULER (1952) finds it hard to consider dopamine as a serious candidate for the synthesis of noradrenaline (see also WEST, 1954)

In the meantime evidence in favour of the scheme has been accumulating In 1953, I was invited by Dr A D WELCH to come to his department at Yale to initiate a study of the biosynthesis of noradrenaline Together with Dr J D DEMIS Dr WELCH and I incubated a solution of DL dopa labelled by C^{14} in the α position



with homogenates of bovine adrenal medulla (DEMIS BLASCHKO and WELCH 1954) After incubation the homogenates were extracted and chromatographed It was found that the bulk of the L dopa had been converted to dopamine This was to be expected from LANGEMANN s findings But there was also always some radioactivity in the noradrenaline and this radioactivity of the noradrenaline remained constant upon recrystallization Two to three per cent of the total radioactivity was recovered as noradrenaline HAGEN (1956) has since confirmed these results he went a step further he isolated the radioactive dopamine after the incubation and he then re incubated it this time with a homogenate of chick suprarenals Subsequent analysis showed that about six per cent of the radio activity could be recovered as noradrenaline after the incubation This experiment gives for the first time unequivocal evidence of conversion of dopamine to noradrenaline

More work is required before we can be certain that this reaction occurs in all species There may be variants of the scheme in some species (e g in Octopus) but it is of interest that NERI HAYANO STONE DORFMAN and ELMADJAN (1956) have recently obtained evidence for the conversion of dopamine to a noradrenaline like material in the bovine adrenal medulla The available evidence thus suggests that the missing link in the scheme of biosynthesis of the pressor amines has now been found

Inhibitors of the enzyme dopa decarboxylase have been studied in a number of laboratories (SOURKES 1954 HARTMANN AKAWIE and CLARK 1955) these studies have added greatly to our knowledge of the enzyme but they have not been of much use in the search for drugs that might lower arterial blood pressure and might thus be of

therapeutic usefulness This is not surprising The biochemist who considers a scheme like that outlined above asks *which is the rate limiting step* in this sequence of reactions? It seems very unlikely that the formation of dopamine from dopa is the rate limiting step There is so much dopa decarboxylase not only in the chromaffin tissue and in nerves but also in other tissues including liver and kidneys The enzyme in the kidney the site where it was first found (HOLTZ *et al* 1938) is probably responsible for the formation of the urinary dopamine the functional significance of this dopamine of renal origin is still entirely unknown the possibility should be considered that dopamine has a regulatory function in the kidneys

Let us now consider the formation of noradrenaline from *dopamine* This reaction is a typical dehydrogenation and it has therefore been studied in the presence of either coenzyme (DPN) or phosphocoenzyme (TPN) The dehydrogenases are the classical objects for the study of competitive inhibition In our view it seems likely that the reaction catalysed by the new enzyme *dopamine dehydrogenase* is the rate limiting step in the formation of pressor amines Competitive inhibitors of this enzyme have not yet been studied but the search for such compounds would appear more promising than the study of inhibitors of dopa decarboxylase when attempts are made to inhibit the formation of pressor amines

2 RELEASE OF AMINES FROM STORAGE GRANULES

It is now well known that both the catechol amines (adrenaline and noradrenaline) and histamine are stored in cytoplasmic granules Before these amines can exert their biological effects they must be released from the sites of storage and appear free in solution in the neighbourhood of the receptors

For those interested in the treatment of arterial hypertension by the use of drugs the mechanism of release of 5 hydroxytryptamine (5 HT) has recently acquired interest this follows from the work of BRODIE and his colleagues (BRODIE PLETSCHER and SHORE 1956 PLETSCHER SHORE and BRODIE 1956 SHORE PLETSCHER and BRODIE 1956) These authors have shown that reserpine releases 5 HT from sites of storage e g the brain the intestine and the blood platelets This work will be discussed in its pharmacological and clinical aspects in greater detail by other contributors to this symposium

In order to understand the mode of attack of reserpine it is

necessary to ask what is known about the mechanism of storage of 5 HT? It has already been pointed out (BLASCHKO, 1956) that the histological evidence suggests that 5 HT is stored in cytoplasmic granules MASSON (1914) the first author to ascribe a specific endocrine function to the enterochromaffine cells has described methods for the study of these granules (MASSON 1932) To the presence of these argentaffine granules the cells owe the name basigranular (CLARA 1928) Histochemical reactions of these granules have been studied for a long time (see LISON 1931) and it *is now known that the same histochemical reactions are also given* by 5 HT (GOMORI 1953)

Together with Dr L MARTINI and Dr J M WALKER Miss HIMMS and I have recently obtained cell free suspensions of the dog's intestinal mucosa with 5 HT activity These suspensions were prepared by homogenising the mucous membrane of the small intestine in 0 3M sucrose Coarse cell fragments unbroken cells connective tissue and cell nuclei were removed by low speed centrifugation and the low speed supernatant which was still opaque and which contained the cytoplasmic granules was subjected to high speed centrifugation A sediment was thus obtained which was found to contain a large fraction of the 5 HT activity of the low speed supernatant This observation shows that 5 HT resembles adrenaline and noradrenaline (BLASCHKO and WELCH 1953) in that it is stored in the cell in granules similar to mitochondria in their sedimentation properties

A full study of the granules carrying 5 HT remains to be carried out This will make it necessary to separate the argentaffin granules from the many other granules present in these sediments For the study of the catechol amines the chromaffin tissue of the adrenal medulla presents an exceptionally favourable material since practically every cell contains catechol amines

Work on the intracellular localization of 5 HT has recently also been carried out at Yale University by Dr N J GIARMAN to whom I am grateful for the permission to mention some very interesting unpublished results He has independently confirmed our observations on the intracellular localization of 5 HT in the intestinal mucous membrane he has found that in brain and in spleen the 5 HT is similarly distributed He has also shown that during incubation *in vitro* of granular suspensions from these tissues in the presence of reserpine the 5 HT is released from the granules upon recentrifugation he has found that the 5 HT was now present in the supernatant fluid

These observations show that the point of attack of reserpine in releasing 5 HT from storage is the argentaffin granule This is in harmony with the idea that the action of reserpine is due to a similarity between the chemical structures of the 5 HT and reserpine molecules

The amine-carrying granules are characterized by the presence of anions not found in other cells or cell organelles in similar concentration The histamine-carrying granules of the mast cells are rich in heparin and the chromaffin granules of the adrenal medulla contain very large amounts of adenosinetriphosphate The characteristic anion present in the argentaffin granules is unknown but it seems likely that there is a specific anion which is in some way connected with the 5 HT releasing property of reserpine

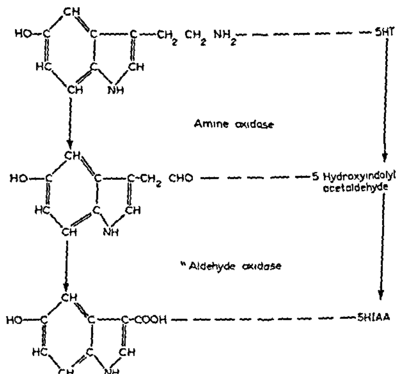
3 INACTIVATION OF AMINES BY AMINE OXIDASE

An increase in the concentration of active substance in the neighbourhood of the receptor can also be brought about by interference with inactivating enzymes The exploitation of such an interference for therapeutic purposes is limited by two factors Firstly in many instances diffusion seems to be an effective means of lowering the concentration of active substance in the neighbourhood of the receptors this is an unspecific process not influenced by drug action Secondly some active substances seem to have several different modes of breakdown and interference with one metabolic pathway may not increase the concentration of free active substance but deflect the breakdown of some of the active material towards different pathways that remain open The potentiation of response to acetylcholine by anticholinesterases shows that under favourable conditions an increase of active substance by inhibition of enzymic inactivation can be achieved Favourable conditions I believe are those in which the distance between receptor and inactivating enzyme is small Also potentiation by drug action appears more easily demonstrable when the concentration of the drug is high this is why it is easier to demonstrate a potentiation of the response to tyramine rather than to 5 HT by Marsilid an inhibitor of the enzyme amine oxidase Tyramine is a less potent amine and more of it has to be given in order to elicit a response

There is no doubt that amine oxidase is a catalyst important for the inactivation of 5 HT This amine is oxidized by the enzyme (FREYBURGER GRAHAM RAPPORT SEAY GOVIER SWOAP and VAN DER BROOK 1952 BLASCHKO 1952a 1953) The metabolic pathway which is initiated by amine oxidase is shown below it

leads from 5 HT, via the corresponding aldehyde to the carboxylic acid 5 hydroxyindoleacetic acid (5 HIAA) This pathway is common to most amines oxidized by amine oxidase (see BLASCHKO, 1952b) 5-HIAA is excreted in the urine, the amount of 5 HIAA excreted has been used as a measure of the amount of 5 HT formed in the body

Pathway of inactivation of 5HT



The possibility of raising the concentration of free 5 HT in the neighbourhood of the receptors by drug action is subject to the limitations already discussed Moreover the problem would be to make such an action selective i e so that the drug reaches the sites of inactivation in the central nervous system without affecting the concentration of 5 HT in the neighbourhood of the peripheral receptors

Some authors believe that amine oxidase is a catalyst which has only one function the biological inactivation of 5 HT (see SJOERDSMA SMITH STEVENSON and UDENFRIEND 1955) It is true that this must be an important function of amine oxidase However I find it difficult to forget the evidence brought forward by SCHAYER and

his colleagues (SCHAYER and SMILEY, 1953 SCHAYER SMILEY, DAVIS and KOBAYASHI 1955) which suggests that amine oxidase has some share in the biological inactivation of adrenaline and noradrenaline I believe amine oxidase has yet another function it is one of the catalysts that removes an excess of dopamine formed I have already mentioned that the potential ability of the organism to form dopamine from dopa seems greatly in excess of the demands for noradrenaline and adrenaline Amine oxidase may ensure that the amount of dopamine converted to noradrenaline and adrenaline is not greater than that required to fill up the depleted stores of these two amines Thus amine oxidase may be one of the factors that take part in the control of the biosynthesis of the two pressor amines

REFERENCES

BLASCHKO H (1939) *J Physiol* 95 30 P
BLASCHKO H (1952a) *Biochem J* 52, x
BLASCHKO H (1952b) *Pharmacol Rev* 4 84
BLASCHKO H (1953) *Brit Med Bull* 9 146
BLASCHKO H (1954) *Pharmacol Rev* 6 23
BLASCHKO H (1956) *CIBA Foundation Symposium on Histamine* pp 381–389 London Churchill
BLASCHKO H and WELCH A D (1953) *Arch exp Path Pharmak* 219 17
BRODIE B B PLETSCHER A and SHORE P A (1956) *J Pharmacol* 116 9
BÜLBRING E (1949) *Brit J Pharmacol* 4 234
CLARA M (1928) *Arch ital Anat Embriol* 25 1
DEMIS D J BLASCHKO H and WELCH A D (1955) *J Pharmacol* 113 14
EULER U S VON (1952) Noradrénaline Symposium sur les hormones protéiques et derivés des protéines II Congrès Internationel de Biochimie Paris SEDES pp 39 55
EULER U S VON HAMBERG U and HELLNER S (1951) *Biochem J* 49 655
FREYBURGER W A GRAHAM B E RAPPORT M M SEAY P H GOVIER W M SWOAP O F and VANDER BROOK M J (1952) *J Pharmacol* 105 80
GOMORI G (1953) *J Histochem and Cytochem* 2, 50
GOODALL McC (1951) *Acta physiol Scand* 24 Suppl 85
HARTMANN W J AKAWIE R I and CLARK W G (1955) *J biol Chem* 216 507
HAGEN P (1956) *J Pharmacol* 116 26
HOLTZ P CREDNER K and KRONEBERG G (1947) *Arch exp Path Pharmak* 204 228
HOLTZ P HEISE R and LÜDTKE K (1938) *Arch exp Path Pharmak* 191 87
HOLTZ P and WESTERMANN E (1956) *Arch exp Path Pharmak* 227 538
LANGEMANN H (1950) XVIIIth Internat Physiol Congress Copenhagen Abstract of Communications p 325
LANGEMANN H (1951) *Brit J Pharmacol* 6 318
LLOYD L (1931) *Arch Biol Paris* 41 343
MASSON P (1914) *C R Acad Sci Paris* 158 59
MASSON P (1932) *Trans Roy Soc Can* 26 Section V p 45
NERI R HAYANO M STONE D DORFMAN R I and ELMADJIAN F (1956) *Arch Biochem* 60 297
PLETSCHER A SHORE P A and BRODIE B B (1956) *J Pharmacol* 116 84

SCHAYER R W and SMILEY R L (1953) *J biol Chem* 202 425
SCHAYER R W SMILEY R L DAVIS K J and KOBAYASHI Y (1955) *Amer J Physiol* 182 285
SCHÜMANN H J (1956) *Arch exp Path Pharmak* 227 566
SHEPHERD D M and WEST G B (1953) *J Physiol* 120 15
SHORE P A PLETSCHER A and BRODIE B B (1956) *J Pharmacol* 116 51
SJOERDSMA A SMITH T E STEVENSON T D and UDENFRIEND S (1955) *Proc Soc exp Biol* 89 36
SOURKES T (1954) *Arch Biochem* 51 444
SOURKES T HENEAGE P and TRANO Y (1952) *Arch Biochem* 40 185
WEIL MALHERBE H (1956) *Biochem J* 63 4 P
WEST G B (1954) *Pharmacol Rev* 6 29

A RECENTLY DEVELOPED SERIES OF GANGLION BLOCKING AGENTS

J W BILLINGHURST

You have already been reminded of the many and varied types of hypotensive drugs which have now appeared and of the growing complexity of structure activity relationships in this field It is not therefore my intention to comment on the general situation but rather to show briefly how one particular series of ganglion blocking compounds is being developed This series which comprises the diquaternaryaminobenzhydryl compounds (ADAMSON *et al* 1956) mentioned by Dr ING has already given rise to at least one very promising hypotensive agent

The compounds with which I will be concerned originated in a project instigated by Dr D W ADAMSON several years ago (ADAMSON *et al* 1949 1950 1951) We were engaged on a search for analgesics antihistamines and spasmolytics *Quaternary ammonium salts of*

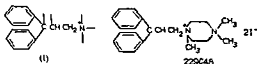


Fig 1

the type (I) (Fig 1) were found to possess powerful atropine like properties One variant of this type of compound 229C48 was found to exert a powerful mydriatic action in mice but unlike atropine had no effect on spasm of the isolated guinea pig ileum caused by acetylcholine

This finding was not followed up immediately because we were at that time developing pyridyl and thienyl analogues of (I) which were of interest as analgesics and antihistamines However a few

years later, Mr A F GREEN discovered that 229C48 was a ganglion blocking agent we therefore turned to the development of this lead

The ethylenediamine analogue 232C53 (Fig 2) was prepared and was found to be rather more active Extension of the benzhydryl sidechain to six carbon atoms gave a compound 288C53, which was considerably more potent and longer acting Hydrogenation of one or both of the phenyl groups to *cyclo*hexyl produced a moderate fall in activity, whilst removal of a phenyl group gave a profound fall in activity Extension of the ethylenediamine chain up to six carbon atoms gave compounds with a somewhat decreased activity, but with an approximately threefold increase of toxicity

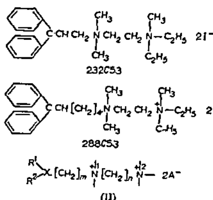


Fig 2

I would add here that recently, our colleague Dr G G COKER has prepared a number of analogues in which the benzhydryl group has been modified by replacing the phenyl groups with thienyl and pyridyl groups, as we did with the monoamino compounds to give analgesics and antihistamines Ganglion blocking activity was again encountered It was found that when R^1 and R^2 were 2 thienyl the activity in general was somewhat lower than when they were phenyl and that when R^1 was phenyl and R was 2 pyridyl, the activity was considerably reduced

Thus we had arrived at a series of compounds of general formula (II) We had found that R^1 and R^2 should preferably be phenyl or substituted phenyl groups and that activities were greatest when the substituents on $\overset{+}{N}{}^1$ and $\overset{+}{N}{}^2$ were no larger than ethyl this also applying when $\overset{+}{N}{}^2$ formed part of a pyrrolidinium piperidinium or morpholinium ring We also found that with these compounds the optimum value for *n* was 2 or 3 in contrast with the methonium

compounds and that as m had been increased from 1 to 7, activity had reached a maximum at $m = 3$ or 4 and had then declined whilst duration of action had progressively increased (Fig 3)

The compound 288C53, which was selected as being representative of the best of these compounds was sent for clinical trial as a hypotensive agent The results were very encouraging the compound being at least as active as pentolinium By this time we had prepared

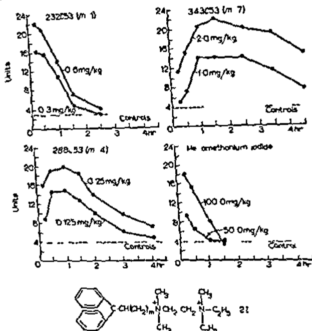


Fig 3

well over one hundred compounds of this series and much had been learned about the structure activity relationships We decided therefore to apply a similar process of modification to other types of compounds possessing benzhydryl groups These included the well known drugs Trasentin (a spasmolytic) diphenhydramine (an antihistamine) and the nitrile (III) which bears similarities to the methadone series of analgesics (Fig 4)

We found that these new types of compounds examples of which are shown in Fig 5 also were powerful ganglion blocking agents However aided by the pharmacological results obtained with the original series we were able to develop these new series reasonably

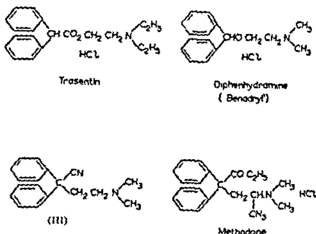


Fig 4

quickly the structure activity relationships running roughly parallel throughout In due course we were in a position to select examples for clinical trial Encouraged by favourable reports on the nitrile 356C54 we have prepared, tested and selected for trial a consider able number of compounds To date the results indicate that the incorporation of a morpholinium group especially in conjunction with a diphenylcyanomethyl group is desirable

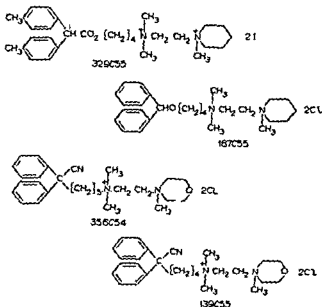


Fig 5

From all this work the compound 139C55 has emerged Its salient structural features are a diphenylcyanomethyl group connected via a chain of four carbon atoms to an ethylene-diammonium group the terminal nitrogen atom of which forms part of a morpholinium ring Clinical results (Locket 1956) suggest that the hypotensive activity of this compound in man is greater and has a more gradual onset and is more prolonged than that of ganglion blocking agents previously available

I would close by saying that much work remains to be done and that we are actively engaged in pursuing this project which appears to be capable of considerable development

REFERENCES

Adamson D W Billinghurst J W Green A F and Lockett S (1956) *Nature* 177 523

Adamson D W (1949) *J chem Soc* S144

Adamson D W (1950) *J chem Soc* 885

Adamson D W and Billinghurst J W (1950) *J chem Soc* 1039

Adamson D W Barrett P A and Wilkinson S (1951) *J chem Soc* 52

Adamson D W Barrett P A Billinghurst J W Green A F and Jones T S G (1951) *Nature* 168 203

Adamson D W Duffin W M and Green A F (1951) *Nature* 167 153

Locket S (1956) *Brit med J* ii 116

BIOCHEMICAL DIVERSITY IN HYPOTENSIVE DRUGS

H McILWAIN

Dr Ing remarked that *chemically* the hypotensive drugs were of widely scattered structures Biochemical information about their modes of action indicates these also to be diverse This can be illustrated by agents whose actions on nervous tissues have been studied in these laboratories

Protoveratrine has major metabolic effects on isolated cerebral tissues at concentrations which are very low and comparable to those at which it is effective in the whole animal Thus at $5-10 \times 10^{-7}$ M (about 0 5 μg/ml) it greatly increases the respiration and aerobic

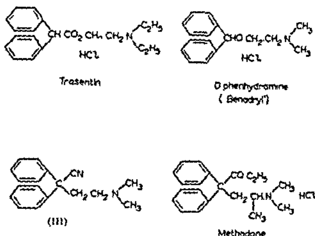


Fig 4

quickly the structure activity relationships running roughly parallel throughout In due course we were in a position to select examples for clinical trial Encouraged by favourable reports on the nitrile 356C54, we have prepared, tested and selected for trial a considerable number of compounds To date the results indicate that the incorporation of a morpholinium group especially in conjunction with a diphenylcyanomethyl group is desirable

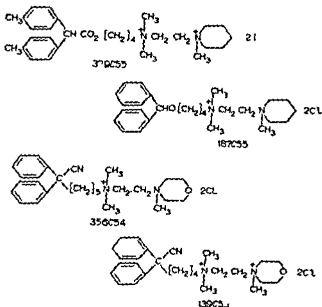


Fig 5

can also form part of a ring We have observed reflex bradycardia hypotension and apnoea after administration to cats and rabbits of for example some 2 amino pyridine and some 4 amino-quinazoline compounds Second in the majority of these new compounds the reflex effects are entirely prevented by cervical vagotomy so that stimulation of carotid sinus receptors which has been postulated in the case of veratrum alkaloids appears to play no part in their action Third the most interesting of these compounds studied in several animal species showed declining action through the series rabbit cat dog and monkey In fact in the majority of monkey tests we were unable to observe any hypotensive action at all and that caused a decline in our interest partly also because all the compounds as also described by Dawes were excessively brief in action

DR J G WIDDICOMBE With regard to the amidine group of compounds it was shown by Dawes that in the dog they produce a considerable hypertension and respiratory stimulation—in other words completely the opposite effect to that seen in cats and rabbits Also although they may have properties in common with the veratrum alkaloids, I do not think it has been shown that they depolarise the nerve membrane which is the characteristic action of veratrum alkaloids

PROFESSOR F H SHIRK Some time ago we were working on some of the lower amidines and we used S methyl isothiourea It is interesting in view of the remarks which have been made that this is quite a powerful pressor agent apparently acting peripherally and also enhancing the response to adrenaline On the other hand if one moves up the series to the higher members it is found that these effects are less prominent and among higher members substances are found with a depressor action We took five or six of these to a clinical trial but they were not practicable For example one of them was hexamethylenediisothiourea which as I gather from subsequent work performed elsewhere releases a certain amount of histamine

DR H J BARBER (Dagenham) I should like to draw Dr Ing out a little on the effect of the anions He commented that it was extremely difficult to understand why the associated anion appears to have some effect on the various actions of the bis quaternary cations Has Dr Ing any hypothesis however far fetched that will give any kind of picture of this effect? It seems very surprising

glycolysis of cerebral tissues, and decreases their anaerobic glycolysis Moreover, this affects the tissues functionally with these concentrations the metabolic response to electrical pulses is greatly increased, when pulses are spaced at intervals of a second or so These actions appear to be due to protoveratrine delaying the reaccumulation of potassium ions in the tissue (WOLLENBERGER, 1955) Reserpine and tetraethylammonium salts have no comparable actions Chlorpromazine, however, has an inhibitory effect in isolated, electrically stimulated cerebral tissues at levels of 10^{-5} M, again comparable to those acting *in vivo* Reserpine has not but here the admirable studies especially of BRODIE and his collaborators have shown displacement of serotonin from different parts of the body including the brain

It is interesting to see that Dr ING places some simpler guanidines and amidines in the same category as the veratrum alkaloids for several other guanidines and amidines are known to have effects on the respiration and glycolysis of cerebral tissues which are, in part similar to that of protoveratrine (DICKENS 1939, GREENGARD and McILWAIN, 1955) As guanidine itself has this property, the hypotensive guanidines and amidines would repay examination

These illustrations together with those of Dr BLASCHKO serve to emphasize the diversity of biochemical modes of action displayed by the hypotensive drugs investigated up to the present

REFERENCES

DICKENS F (1939) *Biochem J* 33 2017
GREENGARD O and McILWAIN H (1955) *Biochem J* 61 61
WOLLENBERGER A (1955) *Biochem J* 61, 68 77

GENERAL DISCUSSION

DR A SPINKS (Manchester) We have examined a very large series of basic compounds related to the compounds producing reflex hypotension described by Dawes Three general points have emerged from this study First we have established similarly to Dawes that the functional group which is important for this action is the amidine group and we have found that apart from being in a chain this group

the salts of mineral acids This led us to examine the effect of sodium stearate and palmitate on the action of Dequadin chloride which they potently antagonised

DR BLASCHKO For some of the active amines the anion appears to be remarkably specific in the site of storage It is well known that in the mast cell histamine is in some way associated with a sulphonic ester and it is equally interesting to know that the catechol amines adrenaline and noradrenaline are stored in granules in which about 50 per cent of the anion is ATP That is to say the anion comes into this picture as a very specific agent

DR ING I am relying on Dr Harington s results I am afraid that I have no explanation whatsoever to offer for them I wonder whether Dr Harington has?

DR M HARINGTON The effect of the anion, to which I think Dr Ing was alluding was on the intestinal absorption of the bis quaternary ammonium derivatives rather than on their pharma cological action We found on giving various hexamethonium salts to human subjects that there was an apparently consistent difference between the absorption of hexamethonium when it was combined with different anions For instance hexamethonium bitartrate was always more poorly absorbed when given by mouth than the bromide or chloride and this was supported by clinical observations Unless it was due to some difference in the make up of the tablets we could form no hypothesis to explain the difference in absorption of hexamethonium when given combined with different anions since the salts should be completely dissociated in the stomach

DR BARBER Salts such as these are more or less completely dissociated in dilute solution and that is a fact which can be estab lished by any physical chemist I think one can only say perhaps that the anion must have an interesting pharmacological effect on the particular receptors which are responsible for the absorption of the cation

DR ING We are very apt to think of absorption by cells as being a passive thing and in the case of these bis quaternary compounds, of the cation passing through some membrane I think it is much more probable really that absorption from the gastro intestinal tract is an active process and it may well be that the quaternary cation cannot be absorbed except in company with some anion If that were true then we should not be dealing with a simple physico chemical transference of a molecule or a cation across a membrane but an active physiological or biochemical process in which the nature of the anion that goes with the cation may alter the ease and rate of its passage across the membrane

DR H O J COLLIER (Ware) We came across an instance recently where the anion appeared to affect the biological activity of the cation Among a number of salts of a bis quinaldinium antibacterial (Dequadin) we found that the stearate and palmitate although soluble had much lower activity against staphylococci *in vitro* than

2ND SESSION

(AFTERNOON)

THURSDAY APRIL 5TH

Chairman Professor J H Burn

THE PHARMACOLOGY OF HYPOTENSIVE DRUGS

SOME PHARMACOLOGICAL DIFFERENCES BETWEEN HYPOTENSIVE DRUGS, WITH SPECIAL REFERENCE TO HYDRALAZINE AND RESERPINE

J TRIPOD

AMONGST all the synthetic or natural substances which produce in the laboratory a fall in blood pressure in normotensive animals there are but few that provoke hypotension of a sufficiently special type to justify their therapeutic use as antihypertensive agents Since the fall in blood pressure is not a sufficient criterion in itself for the choice of an antihypertensive agent the purpose of making a pharmacological analysis of the general and especially circulatory properties of hypotensive drugs is to bring out the particular characteristics which might serve to indicate an antihypertensive action These signs however are extremely difficult to analyse for they depend on a series of factors which apply to special sites of action at the level of the circulatory system or on its hormonal autonomic central or peripheral regulation In other words there exist many ways of approaching the analysis of the mode of action of an antihypertensive agent in the normotensive animal and to this must be added a complex of special mechanisms which come into action in the various forms of experimental and clinical hypertension

Among a great number of pharmacological findings I have preferred to choose those that enable the hypotensive substances to be characterized in acute pharmacological experiments Further more the theme I have been given is the discussion of the two drugs reserpine and hydralazine

For th characterization of these substances certain fields of research have been selected for two reasons

(1) There exists a larger amount of comparative data for them and

(2) They are in my opinion particularly appropriate to establish the pharmacological differentiation of such substances in acute experiments

chosen a few examples which in particular, demonstrate that at l ast the two substances under discussion reserpine and hydrala zine represent two entirely different types of pharmacological effect both as regards their circulatory action and their antihyper tensive effect The same also holds good when these substances are compared with other hypotensive agents

ANT GONISTS	Peripheral vasoconstriction produced by					
	DREN LINE	NOR DREN LINE	HISTAMINE	SEROTONIN	V SOPRESSIN	B Cl₂
HYDR LA INE	10	3 10^{-5}	5 10^{-7}	10^{-6}	3 10^{-6}	5 10^{-4}
RESERPINE	10^{-5}	0^{-5}	10^{-5}	10^{-5}	10^{-6}	10^{-6}
VERATRINE	10^{-5}	5 10^{-5}	$>10^{-4}$	3 10^{-4}	10^{-5}	10^{-5}
PHENTOLAMINE	10^{-7}	5 0^{-8}	10^{-5}	2 10^{-}	$>10^{-4}$	$>10^{-3}$
D GIN	10^{-7}	2 10^{-}	$>10^{-5}$	10^{-8}	10^{-6}	$>10^{-4}$
LSD25	2 10^{-7}	5 10^{-7}	10^{-}	2 10	10^{-10}	5 10^{-8}
TRIPELENN MINE	10^{-5}	10^{-5}	10^{-4}	10^{-}	10^{-5}	10^{-}
CHLO P OMAZINE	2 10^{-6}	10	10^{-}	10^{-4}	10^{-6}	10^{-7}
P VE INE	10^{-6}	10^{-5}	3 10^{-6}	10^{-6}	3 0^{-}	10^{-5}
CETYLCHOLIN	5 10^{-8}	0^{-6}	0^{-}	3 10^{-8}	2 0^{-}	10^{-7}

□ goonism ■ ner

Fig 1 Effect of various drugs on peripheral vasoconstriction produced by adrenaline noradrenaline histamine serotonin vasopressin, and $BaCl_2$ The values given in the squares correspond to concentrations producing roughly a 50 / antagonistic effect

In the case of the vessels of the isolated hind legs of the rabbit one is already aware of some differences in the spectrum of the specific vascular antagonisms of hydralazine and reserpine (TRIPOD and MEIER 1954b 1954c MEIER et al 1954) If this study is extended to cover various substances producing a particular vascular response a wider basis of comparison is obtained (Fig 1)

Thus in this test where the site and mechanism of the peripheral vascular action are not masked by autonomic hormonal or central

EVALUATION OF HYPOTENSIVE ACTION

Naturally, the first step is to try and approach the acute hypotensive action as such However, our own investigations and those of other pharmacologists have shown that not every and any type of hypotension is appropriate for therapeutic use In the case of the acute hypotensive effect in the normotensive animal one must first of all evaluate the course and duration of the fall of blood pressure Thus MEIER *et al* (1954, 1955) have recently shown that hypotensive drugs may be classified into three groups

Those for which the intensity of the hypotensive effect depends on the dose acetylcholine histamine veratrine, phentolamine (GROSS *et al* 1951) papaverine and azamethonium (BEIN and MEIER 1951) In this group of substances only a few are therapeutically interesting in certain forms of hypertension

Those for which the duration of the blood pressure effect depends on the dose hydralazine (BEIN *et al* 1953a) and reserpine (BEIN *et al* 1953b BEIN 1956) which have taken on considerable importance in the treatment of hypertension

An intermediary group comprising for instance kallikrein and chlorpromazine (COURVOISIER *et al* 1953) for which a certain relation may be found between the dose and the duration of the hypotension

It would thus appear that in some cases the duration of the fall in blood pressure in the normotensive animal plays a negligible role as a characteristic of an antihypertensive action while for other hypotensive drugs such as hydralazine and reserpine it seems to be an important element of their potential value in therapy Besides these substances others with a long lasting action have been described lately in the group of ganglion blockers (PLUMMER *et al* 1955) Two possibilities may be considered for the significance of this phenomenon namely

(1) That the long duration of effect is an important element in the therapeutic effect or
(2) That the long duration of effect for some substances at least is the outer sign of a biochemical pattern which is also related to the therapeutic effect

SPECIFIC ANTAGONISM TO VASOCONSTRICTOR DRUGS

The analysis of the effects on the circulation and of the overall pharmacological action is a further possible approach I have

chosen a few examples which in particular demonstrate that at least the two substances under discussion reserpine and hydralazine represent two entirely different types of pharmacological effect both as regards their circulatory action and their antihypertensive effect The same also holds good when these substances are compared with other hypotensive agents

ANTAGONISTS	Peripheral vasoconstriction produced by: ADRENALINE	NORADRENALINE	HISTAMINE	SEROTONIN	VASOPRESSIN	$BaCl_2$
HYDRALAZINE	10	$3\ 10^{-5}$	$5\ 0^{-7}$	10^{-6}	$2\ 0^{-6}$	$5\ 10^{-6}$
ESERINE	$>10^{-5}$	10^{-5}	10^{-5}	10^{-3}	10^{-6}	10^{-6}
VERATRINE	10^{-5}	$5\ 10^{-5}$	■ $>10^{-4}$	■ 5×10^{-6}	10^{-5}	■ 10^{-5}
PHENTOLAMINE	10^{-7}	$8\ 0^{-8}$	10^{-5}	$2\ 10^{-}$	■ $>10^{-4}$	■ $>10^{-5}$
MYDE C H	?	10^{-7}	■ $>10^{-4}$	10^{-8}	10^{-6}	■ $>10^{-6}$
LSD_{25}	$3\ 10^{-7}$	■ 5×10^{-9}	10^{-6}	$2\ 10^{-}$	■ 10^{-10}	■ 5×10^{-5}
TRIPELENNAMINE	10^{-5}	-5	10^{-}	10^{-}	10^{5}	10^{-4}
CHLORPROMAZINE	$2\ 10^{-6}$	10^{-7}	$4\ 10^{-}$	10^{-}	10^{-4}	10
PAPAVERINE	$7\ 10^{-6}$	10^{5}	$3\ 10^{-6}$	10^{-6}	$5\ 0^{-}$	10^{5}
ACETYLCHOLINE	$5\ 0^{8}$	0^{-}	10	$3\ 0$	$3\ 0^{-6}$	10^{-7}

☐ antagonism ■ no

Fig 1 Effect of various drugs on peripheral vasoconstriction produced by adrenaline noradrenaline histamine serotonin vasopressin and $BaCl_2$ The values given in the squares correspond to concentrations producing roughly a 50 / antagonistic effect

In the case of the vessels of the isolated hind legs of the rabbit one is already aware of some differences in the spectrum of the specific vascular antagonisms of hydralazine and reserpine (TRIPOD and MEIER 1954b 1954c MEIER *et al* 1954) If this study is extended to cover various substances producing a particular vascular response a wider basis of comparison is obtained (Fig 1)

Thus in this test where the site and mechanism of the peripheral vascular action are not masked by autonomic hormonal or central

EVALUATION OF HYPOTENSIVE ACTION

Naturally, the first step is to try and approach the acute hypotensive action as such However, our own investigations and those of other pharmacologists have shown that not every and any type of hypotension is appropriate for therapeutic use In the case of the acute hypotensive effect in the normotensive animal one must first of all evaluate the course and duration of the fall of blood pressure Thus MEIER *et al* (1954 1955) have recently shown that hypotensive drugs may be classified into three groups

- Those for which the intensity of the hypotensive effect depends on the dose acetylcholine histamine veratrine phentolamine (GROSS *et al* 1951) papaverine and azamethonium (BEIN and MEIER 1951) In this group of substances only a few are therapeutically interesting in certain forms of hypertension
- Those for which the duration of the blood pressure effect depends on the dose hydralazine (BEIN *et al*, 1953a) and reserpine (BEIN *et al* 1953b BEIN 1956) which have taken on considerable importance in the treatment of hypertension
- An intermediary group comprising for instance kallikrein and chlorpromazine (COURVOISIER *et al* 1953), for which a certain relation may be found between the dose and the duration of the hypotension

It would thus appear that in some cases the duration of the fall in blood pressure in the normotensive animal plays a negligible role as a characteristic of an antihypertensive action while for other hypotensive drugs such as hydralazine and reserpine it seems to be an important element of their potential value in therapy Besides these substances others with a long lasting action have been described lately in the group of ganglion blockers (PLUMMER *et al* 1955) Two possibilities may be considered for the significance of this phenomenon namely

(1) That the long duration of effect is an important element in the therapeutic effect or

(2) That the long duration of effect for some substances at least, is the outer sign of a biochemical pattern which is also related to the therapeutic effect

SPECIFIC ANTAGONISM TO VASOCONSTRICTOR DRUGS

The analysis of the effects on the circulation and of the overall pharmacological action is a further possible approach I have

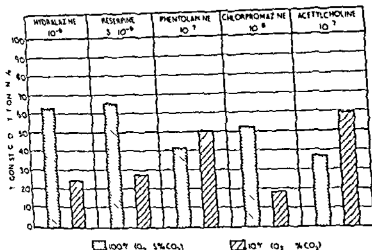


Fig ? Perfusion of the rear extremities of the rabbit Hypoxaemia decreases the vascular antagonism to adrenaline produced by hydralazine reserpine and chlorpromaz ne the effect of phentolamine is only slightly modified but that of a.etylcholine is increased

	PER P ERAL VASOCONSTRICT ON DUE TO			
	ADRENALINE	HISTAMINE	VASOPRESSIN	B Cl_2
HYDRALAZINE	<	>	>	< (REVERSAL)
RESERP NE	<	=	>	=
TR PELENNAM NE		=		
PHENTOLAM NE	=			
PAP VER NE			≥	<
CHLORPROMAZ NE	<	>	=	<
ACETYLC OLINE	>	>	>	>

Fig 3 Perfusion of the rear extremities of the rabbit Effect of 10 / hypoxaemia on various types of vascular antagonistic dilatation

blocking agent an antihistaminic or papaverine are only slightly modified (Fig 3)

This latter series of tests reveals a new possibility of differentiating hypotensive drugs even if it is only fragmentary as yet it brings out

regulation tripelennamine (MAYER *et al*, 1945) is characterized by an exclusive antagonism towards histamine whereas sympathetic blocking drugs such as phentolamine and the ergot derivatives act mainly as antagonists to sympathomimetics and serotonin whilst tending to have a synergistic effect on musculotropic vasoconstriction produced by vasopressin and especially $BaCl_2$ Chlorpromazine and, to a less degree, papaverine are polyvalent spasmolytics in which the antagonisms to histamine and serotonin are predominant But acetylcholine a potent antagonist of all these types of peripheral vasoconstriction differs from the other agents in that its effects are abolished in each case by atropine This predominance of a cholinergic mechanism is of certain theoretical importance Finally the spectrum of the specific antagonisms exerted by hydralazine and particularly reserpine is found rather wanting in specificity It is therefore obvious that certain hypotensive drugs fall into specific pharmacological groups whereas others have a more or less wide range pattern or combinations of antagonistic effects But it is also obvious that this systematic investigation of the peripheral vascular effects is not able to define the particular properties which make an antihypertensive agent out of a given hypotensive substance

EFFECT OF HYPOXAEMIA

However the aforesaid results depend to a certain extent on experimental conditions or on differences in what might be termed the internal medium of the preparation For instance we have recently reported that vascular reactivity for some vasoconstrictor agents depends in certain cases on the Mg and Ca ions on the Na K ratio as well as on hypoxaemia (MEIER and TRIPOD 1955 TRIPOD and WIRZ 1955) Several investigations made in relation to the aforementioned vascular antagonisms also reveal that in the case of adrenaline for instance hypoxaemia reduces the antagonistic action of hydralazine chlorpromazine and reserpine to a great extent whereas the antagonistic effect of phentolamine remains practically unaffected and that of acetylcholine is increased (Fig 2)

In the case of other vasoconstrictor substances results may sometimes be the reverse It is striking however that the effects of acetylcholine are always enhanced which again places this substance in a special position among hypotensive agents As regards hydralazine hypoxaemia appears to influence it more than it does reserpine whereas the specific antagonisms exerted by a sympathetic

of pecificity of this reaction between hydralazine and a protein and/or tissue substrate as well as the pharmacological role of this reaction remain unknown This neutralization however must have some connection with the chemical structure of hydrala zine or even with the properties that are responsible for the long

TREATMENT OF HYDRALAZINE INCUBATION IN	BLOOD PRESSURE FALL mmHg	
1 NaCl 0 9%	-35	>60
ULTRAFILTRATE OF THE RABBIT'S SERUM	20	>30
2 PLASMA (RABBIT)	Ø	Ø
(HUMAN)	Ø	Ø
SERUM (RABBIT)	Ø	Ø
(OX)	6	>30
(SHEEP)	16	7
(PIG)	36	1
(HORSE)	48 (qualitative changes)	>60
3 EGG WHITE 50 %	Ø	Ø
PROTEIN HYDROLYSATE 3 3% (AMIGEN)	Ø	Ø
GROUND ARTERIAL TISSUE (OX) 33 /	Ø	Ø
CASEIN 8 /	40	>60'
HYDROLYSATE 5 / (PROTOLYSATE)	30	>60
PEPTONE 8 /	-33	>25
VU-MIXTURE OF AMINOACIDS 10%	40	>60
VASOPRESSIN 50 U	40	>60
4 GLUCOSE 10%	Ø	Ø
$CuSO_4$ 0 3%	Ø	Ø

Fig 4 The incubation of hydralazine in some media is able to abolish entirely the blood pressure fall in the rabbit provoked by hydralazine 0 5 mg kg i v

duration of the hypotension since amongst a series of hydralazine derivatives those that produce a long lasting hypotension are the ones to be neutralized by the serum (Fig 5)

Other hypotensive agents that belong to the most varied pharma cological or chemical types and especially reserpine do not show thi phenomenon which may therefore be used as a provisional characterization of these substances or possibly even help to explain the multiplicity of the effects of hydrazinophthalazine drugs by a particular reactivity with various elements of the organism (proteins carbohydrates metallic ions etc) in such a way that their hypo tensive effect is modified or even abolished

the importance of the internal medium for vascular reactivity in addition to extrinsic factors connected with the chemical constitution of antihypertensive drugs

RESERPINE AND HYDRALAZINE

I do not intend to discuss in detail the analysis of the site of action on the circulation of the intact animal Reserpine with a more central and hydralazine with a more peripheral mechanism of action are clearly different in their effects Reserpine, which will be discussed later by Dr M VOGT seems to be connected with a mechanism related to serotonin as well it appears that there is no parallel between the content of reserpine in the brain and its duration of action, and that the onset of its action does not coincide with the time at which the maximum concentration is reached in the brain (SHEPPARD *et al* 1955) It would thus seem that an indirect mechanism plays a substantial part here

NEUTRALIZATION OF ACTION OF HYDRALAZINE BY SERUM

On the other hand we have devoted a good deal of time to the task of investigating the mode of action of hydralazine Thus, a recent investigation has shown that the fall in blood pressure produced by hydralazine may be entirely abolished by previous incubation in certain sera (TRIPOD and MEIER 1954a MEIER *et al* 1955) The same holds good for a carbohydrate and a metallic ion whereas, after incubation in another serum the type of hypotension may undergo a great modification but is not suppressed The *in vitro* reaction of hydralazine with arterial tissue various proteins polypeptides etc shows that in spite of its great chemical reactivity thi substance is not linked in each case in an identical manner to a specific chemical element (Fig 4)

Furthermore hydralazine may still be detected chemically in the serum even though the electrophoretic pattern of the serum or the sedimentation constant obtained after ultracentrifugation remains virtually unaltered (ROMETSCH 1956) These last two observations show that this is not a gross modification of serum proteins with formation for instance of proteinic molecular complexes So far it has not been possible to localize hydralazine in any one fraction of serum after hydrolysis precipitation or extraction by various methods (ROMETSCH 1956) so that the nature and degree

yield a complicated spectrum of antagonisms to acute artificial increases in blood pressure This is also the case in animals with chronic hypertension where according to GROSS *et al* (1955) the spectrum of antagonisms exerted by reserpine and hydralazine may vary considerably depending on the treatment of the hypertensive rat and especially on the type of experimental hypertension (renal due to cortexone + NaCl or to cortisone) However the study of these curative and/or protective effects in animals with chronic hypertension has not as yet reached such an advanced state as to permit decisive conclusions to be drawn regarding the mode of action of antihypertensive substances

Nevertheless I believe that the principle of pharmacological analysis shown here by means of a few examples in normotensive animals or normal organs may be applied in a similar manner to the study of the therapeutic effect in the hypertensive animal in order to try and discover in the latter as well the relative importance of the properties of a substance or the active factors that are ultimately essential for the therapeutic effect

REFERENCES

BEIN H J and MEIER R (1951) *Schwei Med Wschr* 81 441

BEIN H J GROSS F TRIPOD J and MEIER R (1953a) *Schweiz Med Wschr* 83 336

BEIN H J GROSS F TRIPOD J and MEIER R (1953b) *Schwei Med Wschr* 83 1007

BEIN H J (1956) *Pharmacol Rev* in press

COURVOISIER S FOURNEL J DUCROT R KOLSKY M and KOETSCHET P (1953) *Arch Int Pharmacodyn* 92 105

GROSS F TRIPOD J and MEIER R (1951) *Sch ei Med Wschr* 81 352

GROSS F SCHULER W TRIPOD J and MEIER R (1952) *Experientia* 8 229

GROSS F (1955) *Klin Wschr* 33 1113

GROSS F NOELPP B SULSER F DOEBELIN R and KÜNDIG H (1955) *Klin Wschr* 33 372

MAYER R L HUTTRER C P and SCHOLZ C R (1945) *Science* 102, 93

MEIER R TRIPOD J and BRUNI C (1954) *Arch exp Path Pharmak* 223 338

MEIER R BEIN H J GROSS F and TRIPOD J (1954) 3rd Internat Congress for Internal Medicine Stockholm

MEIER R and TRIPOD J (1955) 2nd Internat Congress for Angiology Fribourg

MEIER R TRIPOD J and BRUNI C (1955) *Arch Int Pharmacodyn* 101 158

PLUMMER A J TRAPOLD J H SCHNEIDER J A MAXWELL R A and EARL A E (1955) *J Pharmacol* 115 172

ROMETSCH R (1956) personal communication

SHEPPARD H LUCAS R C and TSIEN W H (1955) *Arch Int Pharmacodyn* 103 256

SCHULER W and MEIER R (1955) *Helv Physiol Acta* 13 106

TRIPOD J and MEIER R (1954a) *Helv Physiol Acta* 12 C33

TRIPOD J and MEIER R (1954b) *Arch Int Pharmacodyn* 99 104

TRIPOD J and MEIER R (1954c) *Arch Int Pharmacodyn* 97 251

TRIPOD J and WIRZ E (1955) *Arch Int Pharmacodyn* 102 335

A similar type of formation of complexes may be found with enzymes such as di and mono aminoxidase and the reversal of the reaction by specific metallic ions (Gross *et al*, 1952 Schuler and Meier 1955)

		DOSE mg/kg	BLOOD PRESSURE FALL mmHg WITHOUT CUB TION	AFTER INC BA ION
	1 HYDRAZINO PHTHALAZINE (APRESOLNE)	0·5	35 60	NO E
	1 4 D HYDRAZINO PHTHALAZINE (NEPRESOL)	0 5	30 60'	NONE
	3 PHEN L 6 H DRAZ NO PYR DAZINE (N 6084)	0·3	19 60	NO E
	1 HYDRAZINO 4 BENZYL PHTHALAZ NE (N 6634)	0 3	-24 100'	NONE
	1 HYDR ZINO ISOQUINOLINE (N 7406)	0 3	22 60'	NONE
	3 (*p* C LOROPHEN L) 6 HYDRAZI O P R DAZ E (N 12667)	0 3	24 60'	NONE
	4 HYDRAZINO QU AZOLINE (N 7482)	50	28 20	24 30'
	2 YDR Z NO 3 P EN QU NOXALINE (N 2572)	10	12 0 5	2
	2-HYDRAZ O QUINOL NE (N 12664)	20	44 2	44 1

Fig 5 In the rabbit only the blood pressure fall due to long acting hydrazines is abolished by incubation in the rabbit s serum

This last series of observations again proves clearly that not only are the pharmacological effects of reserpine and hydralazine of an entirely different type but that the biochemical mechanisms of their action also differ

* * * *

There is no doubt that the various analyses reported here are but a fragmentary part of the overall pharmacological study of hypo tensive substances *An important step consists in examining them* reserpine and hydralazine in particular in animals with acute or especially chronic experimental hypertension Thus according to Meier *et al* (1954) and Gross (1955) these hypotensive substances

DR TRIPOD We have tried to do it but we have not succeeded

DR H BLASCHKO May I ask Dr Tripod whether his attempts to regain the hydralazine also included dialysis?

DR TRIPOD They did and there was still neutralization after ultrafiltration I am sorry that for the time being I must give you such negative replies We are in the middle of these investigations and frankly it is to-day difficult to understand fully what they mean It seems that many sorts of protein may be bound to some extent with hydralazine as also copper and glucose—but not all carbo hydrates On the other hand we have never seen a similar effect with reserpine or other hypotensive drugs investigated

GENERAL DISCUSSION

DR A SPINKS I wonder whether this inactivation of hydralazine by incubation with serum is not simply a matter of hydrazone formation from glucose present in the serum?

DR TRIPOD I do not think so because our chemists were able to find the same amount of hydralazine in the blood before and after this neutralization I think it is only a pharmacological neutralization and not the formation of a new chemical compound as far as I know

DR B HOOD Was this inactivation also found with ultrafiltrates of serum?

DR TRIPOD No

SIR CHARLES HARINGTON You showed in one of your illustrations that you got this neutralization with a protein hydrolysate but not with a mixture of amino acids Surely that should give you a new lead as to a likely reacting substance

DR TRIPOD We also investigated some protein hydrolysates having a mixture of peptides and polypeptides Neutralization was only partial not complete as it is in the case of serum plasma or peptone for example

SIR CHARLES HARINGTON What is the essential difference if these were incomplete protein hydrolysates containing peptides of various sizes as distinct from a mixture of individual amino acids?

DR TRIPOD We have not yet done very much with the various peptides or polypeptides We have been more interested in the different types of effect observed with the serum proteins of different animal species

DR W S PEART You say that you were able to find hydralazine still present in the plasma after the incubation even though the pharmacological activity had gone Have you been able to get back that pharmacological activity by any manoeuvre? Presumably this must happen by some means in the body

THEORIES CONCERNING THE SITE AND MODE OF ACTION OF RESERPINE

MARTHE VOGT

SITE OF ACTION

IN discussing the site of action of reserpine I propose to deal with 4 main actions

The fall in blood pressure the sedation the skin flushes and nasal congestion and the effects on the gastrointestinal tract

(1) *Hypotension* There appears to be general agreement that the fall in blood pressure is of central origin there is no direct effect on vascular musculature little sympatholytic effect no ganglion blocking action and no effect on the spinal animal (BEIN *et al* 1953) Rises in blood pressure elicited by carotid occlusion or by stimulation of afferent fibres in the vagus or sciatic nerve are depressed as are pressor effects of electrical stimulation of the medulla and according to some authors of the hypothalamus (BHARGAVA and BORISON 1955 not seen by SCHNEIDER 1955) Since some effects persist after mid collicular section the hypothalamus is not the only central site of action

(2) *Sedation* Concerning the sedation the difference between the effects of reserpine ard those of barbiturates has been most frequently stressed Apart from the observation that sedation with reserpine only rarely leads to sleep the e e g is very different RINALDI and HIMWICH (1955) observed the dis appearance of large amplitude slow waves characteristic of barbiturate effect and of natural sleep when large doses (2 mg reserpine kg) were given intravenously to rabbits Very similar observations recording the disappearance of spon taneous spindles and slow waves in rabbits were recently mad by GANGLOFF and MONNIER (1955) after the intravenous injection of 1 5 mg reserpine per kg Both groups of workers interpreted these changes as an alert pattern of the e e g Another possibility will be discussed later

high concentrations of this substance Further support for the theory was obtained by the finding (PLETSCHER SHORE and BRODIE 1956) that all Rauwolfia alkaloids which have a tranquillizing action are also releasers of 5 HT

Let me now discuss whether the main actions of reserpine could in the light of present knowledge be explained as results of the release into the blood stream of large amounts of 5 HT from its places of storage Needless to say that such a discussion will be handicapped by the incomplete knowledge of the pharmacology of 5 HT and by the fact that no information whatsoever exists on the possible effects on the tissues which normally store 5 HT of the loss of this cell constituent Since two of these organs the intestinal tract and the brain stem are greatly affected by reserpine the lack of such information may seriously mislead us and I hope that future experiments attempting to correlate tissue concentrations of 5 HT with possible changes in function will clarify that point A single observation on this question is at present available it is the fact of a reduction to one half in the 5 HT content of the dog s hypothalamus by sublethal doses of amphetamine (PAASONEN and VOGT 1956) The signs exhibited by these dogs are of course those of excitement and therefore the opposite of those after reserpine No conclusion can at present be drawn from such an isolated fact particularly not regarding the question whether complete loss of 5 HT as seen after reserpine renders the brain stem incapable of normal function

That 5 HT affects impulse transmission and may therefore influence the function of nervous centres is shown by experiments on the superior cervical ganglion (TRENDELENBURG 1956) in which transmission is enhanced and on the cerebral cortex (MARAZZI and HART 1955) in which transmission is said to be impaired Unfortunately both these structures contain no or little 5 HT and information on centres containing high stores of 5 HT is completely lacking

The only information I have found on the action of reserpine on central synapses is that of an increase in monosynaptic action potentials in the spinal cord of the cat after a large dose (5 mg/kg) of the drug (SCHNEIDER *et al* 1955)

A theory which explains central actions of reserpine by high levels of circulating 5 HT assumes that 5 HT passes the blood brain barrier The view however that 5 HT does not penetrate into the brain after parenteral administration has been put forward by WOOLLEY and SHAW (1954) who were unable to detect 5 HT in the

Reserpine abolishes sham rage in cats in which it has been produced by decortication and section of the brain stem through the anterior hypothalamus (SCHNEIDER, 1955) This demonstrates that the posterior hypothalamus is one of the sites at which sedation can take effect

(3) *Flushes* of the face and arms and nasal and conjunctival vasodilatation are common side effects of reserpine therapy (FREIS and ARI 1954) Their origin has not been analysed except for the observation that they do not yield to anti histamines

In animals miosis relaxation of the nictitating membrane (BEIN 1953) and ptosis of the eyelids are prominent effects of reserpine They are not due to direct action on the musculature and are usually described as due to inhibition of sympathetic tone

(4) The *increase in intestinal motility* most prominent in the dog but also seen in man is not of central origin since it persists after section of the cord and vagotomy yet it is not elicited in an isolated preparation suspended in an organ bath (PLUMMER BARRETT and RUTLEDGE 1955)

MODE OF ACTION

One of the most characteristic features of the action of reserpine is its long latent period even after intravenous administration the effects take at least an hour to develop unless the dose has been extremely high This suggests that it is not the reserpine molecule itself which is responsible for the effects but either a metabolite or a substance produced in the body by the reserpine All known reserpine metabolites are products of hydrolysis which have no strong pharmacological action (PLUMMER BARRETT and RUTLEDGE 1954) The second possibility has found much support from the observation (PLETSCHER SHORE and BRODIE 1955) that reserpine releases 5 hydroxytryptamine (5 HT) from the intestine followed by the discovery that it also releases 5 HT from platelets and from brain (PLETSCHER SHORE and BRODIE 1956 PAASONEN and VOGT 1956) Considering these findings together with the observation (SHORE SILVER and BRODIE 1955) that reserpine and 5 HT both potentiate the action of hexobarbitone in mice BRODIE and his collaborators came to the conclusion that the central actions of reserpine might well be due to the release of large quantities of 5 HT from its body depots a release which would expose the tissues to

on the peripheral actions of 5 HT whereas central actions are either not antagonized or only influenced by large doses (GADDUM and VOGT 1956) The interpretation of the gastro-intestinal effects of reserpine as a peripheral action of circulating 5 HT would also serve to explain the paradoxical observation that the actions persist when all connections with the cord have been severed and yet cannot be elicited in the isolated organ suspended in a bath

Antagonists Any attempt to explain the central effects of reserpine by a flooding of the brain with 5-HT will fail if it can be shown that the effects of administration of 5 HT and of reserpine are not antagonized by the same drugs Experiments on antagonists were done on cats given 5 HT into the cerebral ventricles or reserpine intraperitoneally (GADDUM and VOGT 1956) and in mice injected parenterally with either drug (SHORE SILVER and BRODIE 1955) It was shown in the cat that lysergic acid diethylamide (LSD) morphine and methadone interrupted the lethargy induced by either 5 HT or reserpine It was found in the mouse that LSD antagonized the synergism between hexobarbitone and 5 HT in the same way as that between hexobarbitone and reserpine These facts add circum stantial evidence to the view that some at least of the central effects of reserpine are indeed mediated by a raised level of circulating 5 HT

The complexity of the phenomena involved in the action of reserpine should however not be forgotten and may be illustrated by the following examples not only is th 5 HT concentration in the hypothalamus reduced by reserpine its noradrenaline content is also considerably lowered (HOLZBAUER and VOGT 1956) there is however no general liberation of noradrenaline from tissues as is shown by the fact that the denervated adrenal medulla loses none of its amines when 0 4 mg/kg reserpine is given Another compli cation arises from the fact that pronounced tolerance develops towards 5 HT whereas no such tolerance seems to arise from prolonged treatment with reserpine (WILKINS 1954)

I wish to con lude this survey by a last instance of apparent correlation between the actions of 5 HT and of reserpine It con cerns the alert e e g reported by RINALDI and HIMWICH (1955) and by GANGLOFF and MONNIER (1955) in rabbits injected intra venously with reserpine GUNN SAWYER and VOGT (unpublished ob ervations) took electroencephalographic records of cats from leads inserted into many parts of the brain and compared the e e g before and after the injection of 5 HT (0 75 mg) into the cerebral ventricles Many regions including some areas of the cortex and of

brain of the mouse after having given 5 mg intraperitoneally It is difficult to accept this view for the mouse in which central effects are produced by large doses in other species the parenteral administration is limited by the serious vascular effects produced so that the theory cannot easily be put to the test In man tumours of the enterochromaffin tissue, while causing greatly elevated concentrations of 5 HT in the blood have not been reported to produce central effects In view however of the rapid excretion of the drug and the ease with which tolerance develops the lack of cerebral signs does not prove conclusively that 5 HT does not penetrate into the brain Obviously, direct experiments will have to be carried out to decide this point

(1) Taking the effects of reserpine in the order in which I discussed their site of action the first question would be whether the hypotension of central origin may be explained by a flooding of the organism with 5 HT

Except in the mouse which tolerates large doses of 5 HT cerebral effects have only been elicited in the experimental animal by injection into the cerebral ventricles (FELDBERG and SHERWOOD 1954 GADDUM and VOGT 1956) The blood pressure was not studied in any of these experiments so that direct evidence is not available on the possibility of hypotension being produced by an excess of circulating 5 HT

(2) Concerning the sedation the position is more favourable The mouse becomes less lively after a dose of 5 HT and its sleeping time following the administration of barbiturates is prolonged The cat becomes retiring lethargic and shows diminishing muscular tone the same effects are produced by reserpine There are however features of reserpine poisoning which are not seen after an injection of 5 HT into the cerebral ventricle These are miosis relaxation of the nictitating membrane and ptosis of the eyelids Either these effects of reserpine are not mediated by a release of 5 HT or the 5 HT injected into the ventricle does not reach the sites responsible for these phenomena

(3) and (4) Many side effects of reserpine therapy such as flushes nasal and conjunctival vasodilatation and diarrhoea resemble those of administration of 5 HT to animals or the signs found in patients suffering from carcinoid tumours There is thus no difficulty in attributing these effects to circulating 5 HT and a rational therapy might give up trying to antagonize these effects with antihistamines and should seek to employ antagonists of 5 HT instead this is somewhat hopeful since small doses of such antagonists are active

We also did this on an innervated perfused hind limb preparation in rabbits using a washed red cell dextran Krebs Henseleit solution mixture which conserves nervous activity and when we injected reserpine into the perfusate we also observed a fall in the perfusion pressure indi ating vasodilatation

The question arises whether this is just an effect which is obtained in the isolated limb or whether it is something which happens in the whole animal

Using this preparation of a rabbit s hind limb perfused with the red cell dextran Krebs Henseleit mixture and connected to the remainder of the animal only by nervous pathways we injected reserpine into the upper part of the animal In this case as the blood pressure falls in the upper half of the animal the perfusion pressure in the hind limb actually rises We have repeated this experiment on many occasions It would appear therefore that the hind limb has been exposed to an increase not a decrease in the number of nervous impulses We explain this by assuming that in the rabbit the peripheral action of reserpine is important but the homeostatic mechanisms which operate in the whole animal antagonise the fall in pressure and produce a state of vaso constriction in the hind limb

DR B K BHATTACHARYA (London) For some time past Lewis and I at the National Institute for Medical Research have been working on the release of 5 hydroxytryptamine (5 HT) by histamine liberators We found that histamine liberator Compound 48/80 released not only histamine but 5 HT as well from the perfused hindquarters of the rat We worked with reserpine to see whether it liberated 5 HT or not but found no effect in acute experiments When the rats had been treated with intraperitoneal injections of reserpine (5 mg/kg) for two or three days intra arterial injection of 48/80 into the perfused hindquarters of the rat released the usual amount of histamine but no 5-HT or only a minute amount This means that there is ome interrelationship between 5 HT and reserpine Reserpine depletes not only the rat s intestinal tract of 5 HT but also a number of organs like brain and platelets If we perfuse the rat s intestine we do not get any 5 HT released by reserpine This mean that reserpine takes a long time to be metabolised in the body—six to eight hours twelve hours maybe

DR P B BRADLEY (Birmingham) As regards the E E G effects produced by reserpine and intraventricular injections of 5 HT we have observed with both these drugs that it is possible to obtain an

the hypothalamus showed a gradual disappearance of the high voltage slow waves The e e g reminiscent in its early phases of arousal , flattened more and more and finally suggested depression of all activity rather than alertness ' The process was reversible, but only after 4–5 hours It seemed to us that there was great resemblance between our records and those published by RINALDI and HIMWICH and by GANGLOFF and MONNIER and we would like to suggest that possibly neither of them constitute typical alertness or arousal

REFERENCES

BEIN H J (1953) *Experientia* 9 107
BEIN H J GROSS F TRIPOD J and MEIER R (1953) *Schweiz Med Wschr* 83 1007
BHARGAVA K P and BORISON H L (1955) *J Pharmacol* 115 464
FELDBERG W and SHERWOOD S L (1954) *J Physiol* 123 148
FREIS E D and ARI R (1954) *Ann N Y Acad Sci* 59 45
GADDUM J H and VOGT M (1956) *Brit J Pharmacol* 11 175
GANGLOFF H and MONNIER M (1955) *Experientia* 11 404
HOLZBAUER M and VOGT M (1956) *J Neurochem* 1 8
MARAZZI A S and HART E R (1955) *Science* 121 365
PAASONEN M K and VOGT M (1956) *J Physiol* 131 617
PLETSCHER A SHORE P A and BRODIE B B (1955) *Science* 122 374
PLETSCHER A SHORE P A and BRODIE B B (1956) *J Pharmacol* 116 46
PLUMMER A J BARRETT W E and RUTLEDGE R A (1954) *Fed Proc* 13 395
PLUMMER A J BARRETT W E and RUTLEDGE R (1955) *Amer J Digest Dis* 22 337
RINALDI F and HIMWICH H E (1955) *Ann N Y Acad Sci* 61 27
SCHNEIDER J A (1955) *Amer J Physiol* 181 64
SCHNEIDER J A PLUMMER A J EARL A E and GAUNT R (1955) *Ann N Y Acad Sci* 61, 17
SHORE P A SILVER S L and BRODIE B B (1955) *Science* 122 284
TRENDELENBURG U (1956) *Brit J Pharmacol* 11 74
WILKINS R W (1954) *Ann N Y Acad Sci* 59 36
WOOLLEY D W and SHAW E (1954) *Proc Nat Acad Sci* 40 228

GENERAL DISCUSSION

PROFESSOR F H SMIRK I would like to refer briefly to some work which has been carried out in Dunedin by Drs Doyle McQueen Blackman, Gallagher and myself We perfused rat hindquarters at a constant rate and recorded changes in the perfusion pressure We raised the perfusion pressure with barium chloride noradrenaline or vasopressin and then administered reserpine Under these conditions we found that reserpine caused peripheral vasodilatation

We also did this on an innervated perfused hind limb preparation in rabbits using a washed red cell dextran Krebs Henseleit solution mixture which conserves nervous activity and when we injected reserpine into the perfusate we also observed a fall in the perfusion pressure indicating vasodilatation

The question arises whether this is just an effect which is obtained in the isolated limb or whether it is something which happens in the whole animal

Using this preparation of a rabbit s hind limb perfused with the red cell dextran Krebs Henseleit mixture and connected to the remainder of the animal only by nervous pathways we injected reserpine into the upper part of the animal In this case as the blood pressure falls in the upper half of the animal the perfusion pressure in the hind limb actually rises We have repeated this experiment on many occasions It would appear therefore that the hind limb has been exposed to an increase not a decrease in the number of nervous impulses We explain this by assuming that in the rabbit the peri pheral action of reserpine is important but the homeostatic mechan isms which operate in the whole animal antagonise the fall in pressure and produce a state of vaso constriction in the hind limb

Dr B K Bhattacharya (London) For some time past Lewis and I at the National Institute for Medical Research have been working on the release of 5 hydroxytryptamine (5 HT) by histamine liberators We found that histamine liberator Compound 48/80 released not only histamine but 5 HT as well from the perfused hindquarters of the rat We worked with reserpine to see whether it liberated 5 HT or not but found no effect in acute experiments When the rats had been treated with intraperitoneal injections of reserpine (5 mg kg) for two or three days intra arterial injection of 48/80 into the perfused hindquarters of the rat released the usual amount of histamine but no 5 HT or only a minute amount This means that there is some interrelationship between 5 HT and reserpine Reserpine depletes not only the rat s intestinal tract of 5 HT but also a number of organs like brain and platelets If we perfuse the rat s intestine we do not get any 5 HT released by reserpine This means that reserpine takes a long time to be metabolised in the body—six to eight hours twelve hours maybe

Dr P B Bradley (Birmingham) As regards the E E G effect produced by reserpine and intraventricular injections of 5 HT w have observed with both these drugs that it is possible to obtain a

increase in the amount of slow activity in the E E G , but we believe that the conditions under which the recording is made are rather important here Whereas with barbiturates for example one gets the typical pattern of electrical activity irrespective of whether the animal is in the open laboratory or enclosed in a soundproof room with these drugs one only sees the slow activity if the animal is kept in an environment which is free from external stimuli Under those conditions we have observed that there is in some cases with these drugs an increase in the amount of slow activity It is not perhaps as much as one would expect from the sedation produced

Although there is some similarity between the effects of these drugs there are also quite frequent differences Reserpine seems to produce more direct sedation of the animal I do not know whether Dr Feldberg will bear me out on this but I believe he has described the effects of intraventricular 5 HT as being a muscular weakness apart from sedation and we have observed similar effects ourselves

DR VOGT May I ask which doses were used because I think that is most important? The doses we used were very high doses but you may have worked more in the physiological range

DR BRADLEY The doses of reserpine were quite small of the order of 100–150 µg /kg and similar doses of 5 HT

DR W FELDBERG (London) It is difficult when muscular weakness is produced by an intraventricular injection to know how much sedation there is in the animal at the same time

One point occurs to me if it were possible in cats to deplete the brain of 5 HT with reserpine it would be interesting to see whether in such circumstances the intraventricular injection of 5 HT would have the opposite effect because it seems to me not at all certain whether the central effects of reserpine are an action of the released 5 HT or whether the sedation as well as the depressor effects result from the fact that the brain is depleted of its 5 HT and that there is therefore too little left for its normal function The fact that the action of reserpine is such a long lasting one suggests that the central effects if they have anything at all to do with 5 HT are more likely to be associated with loss of 5 HT from these structures on the other hand the peripheral effects like flushing may well be an effect of released 5 HT

DR VOGT We have tried once to give the two together we have

injected 5 HT into the ventricles 19 hours after intraperitoneal reserpine and have only observed synergism What is absolutely essential is to have both in the brain and in the intestine a parallel estimation of content of the active drugs and state of the animals This has not yet been done

There is one observation made by Brodie which would favour Dr Feldberg s interpretation but we have not been able to see this in the cat he has only reported it in the rabbit in which he tried to prevent the destruction of 5 HT by giving a large dose of marsilid When he gave reserpine after this dose of marsilid he observed excitation Unfortunately this does not seem to happen in the cat at least not in our hands so that we are still no further in deciding what actually caused the signs depletion or flooding or neither

PROFESSOR J H BURN I would like to ask Dr Vogt if she thinks that the question of the presence of 5 HT in sympathetic ganglia is completely closed Trendelenburg has made the observation that in sympathetic ganglia 5 HT has a very striking potentiating action Supposing reserpine which admittedly has no immediate effect of a ganglion blocking sort were to act very slowly and to remove small amounts of 5 HT from sympathetic ganglia you might have a condition at the end of three or four hours which would explain the fall of blood pressure the relaxation of the nictitating membrane perhaps the bradycardia and so on

DR VOGT Unfortunately as far as the evidence goes at present all we can say is that our most sensitive tests have completely failed to show 5 HT in sympathetic ganglia This is of course never final because when the methods become more sensitive one can go one decimal further

In the past these experiments have been done entirely by assay on uterine musculature and they were always open to the criticism that traces of adrenaline were interfering with the oxytocic activity of 5 HT and that therefore 5 HT in the ganglia might have been missed Recently Paasonen has been able to use another organ namely the heart of a mollusc for these estimations and this organ has the great advantage that there is no interference by adrenaline or noradrenaline since these drugs do not act on this mollusc s heart As this preparation is very sensitive indeed to 5 HT and as the results were entirely negative I feel one can say with certainty that though we may not be able to exclude traces the concentration if 5 HT is there must be extremely low

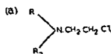
THE β HALOALKYLAMINES

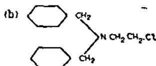
W S PEART

THESE substances are of great interest from a pharmacological point of view since they cause a block in the response to sympathetic nerve stimulation and to sympathomimetic amines which is unique in this field

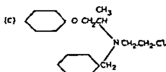
STRUCTURE AND ITS RELATION TO ACTIVITY

The basic chemical structure is illustrated in Fig 1 (a) which shows it to be an N substituted chloroethylamine





Dibenamine (N Dibenzyl chloroethylamine)



Dibenyline (N Phenoxyisopropyl N Benzyl chloroethylamine)

Fig 1

R_1 and R_2 are usually aromatic groups and a typical example of the type of grouping essential for pharmacological activity is shown in Fig 1 (b) This substance is N dibenzyl chloroethylamine or dibenamine (NICKERSON and GOODMAN 1945)

intermediates were the active agents Fig 2 shows one postulated path of degradation The evidence of HARVEY and NICKERSON (1953) on this point is only indirect and a biologically inactive β halo alkylamine gave the same indirect chemical reactions which they suggested indicated ethylenimonium formation The fact that

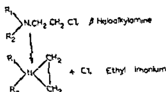


Fig 2

thiosulphate could prevent the block if it was administered before or simultaneously with the β haloalkylamine was used as evidence that such an intermediate was formed since it was known that thiosulphate reacted with similar derivatives of N mustards (see NICKERSON and GUMP 1949 for references) However it will also probably react directly with unchanged β haloalkylamine (HARVEY and NICKERSON 1953) so that overall the evidence in favour of an active intermediate is inconclusive

LONG DURATION OF BLOCK

As the blockade with dibenamine or dibenyline may last 48 hours or more (HECHT and ANDERSON 1947 NICKERSON and GOODMAN 1947 WILBURNE *et al* 1947) the idea of irreversible combination of the drug or an active metabolite with certain components in the receptor cell was postulated (NICKERSON and GOODMAN 1948 NICKERSON and GUMP 1949) This is unlike for example the more usual antagonism between ergotamine and adrenaline where there is a competitive equilibrium type of *inhibition* with antagonism at a definite ratio of these drugs (MENDEZ 1928) With dibenamine however once an *adequate block* has been established it cannot be overcome by massive adrenergic stimulation (NICKERSON and GOODMAN 1947 NICKERSON and NOMAGUCHI 1948) However in the 1–2 hours during which the relatively fixed type of block is developing an equilibrium competitive type of state for dibenamine and adrenaline exists since adrenaline given at this time reduced the subsequent effect of dibenamine (NICKERSON and GUMP 1949) This would indicate that the reaction of β haloalkylamine or an

From a study of a large number of substituted chloroethylamines NICKERSON and GUMP (1949) formulated the supposed structural requirements for biological activity These are

(1) The substance must be a tertiary amine or a quaternary derivative of an active amine
(2) It must include one β haloalkyl group
(3) An unsaturated ring must be attached to the amine
(4) In the case of the benzyl derivatives there must be no sub stitution on the phenyl ring which tends to be out of the plane of the ring

From previous studies it was known that adrenaline blocking actions were possessed in slight degree by phenoxyethylamines (ANAN 1929 BOVET *et al* 1937) and in part this led to the substitu tion of a phenoxy group for a benzyl group in dibenamine The most active of these substances N phenoxyisopropyl N benzyl chloro ethylamine, or dibenyline (Fig 1 (c)) has the important new property of oral activity (FELLOWS *et al* 1954) The factors respon sible for oral activity are unknown

MODE OF ACTION

In general the β haloalkylamines act directly on cells which are receptors for the sympathomimetic amines or the final sympathetic nerve impulses The blockade is therefore completely peripheral and there is no direct interference with sympathetic nerve impulses or circulating sympathomimetic amines Two striking differences in the type of blockade produced compared with all other adrenergic blocking agents are the slow onset of block even on intravenous injection and the prolonged nature of the block once induced NICKERSON who is responsible for the most important work on these compounds has investigated the reasons for these particular properties

POSSIBLE CONVERSION TO AN ACTIVE FORM

Struck by the analogy with the N mustards—in fact NICKERSON and GUMP (1949) report on two N mustards which are potent blocking agents—NICKERSON suggested that the reason for the slow onset of block might be conversion to an active form The N mustards are known to form highly reactive ethyleniminonium and vinyl groups with loss of Cl^- and it was suggested that these

unchanged dibenyline in the urine of dogs after intravenous administration and presented evidence that dealkylation with the formation of the corresponding amine was a major route of degradation

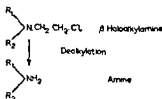


Fig 3

(Fig 3) The N phenoxyisopropyl N benzylamine was then rapidly broken down in other ways

SPECIFICITY

The β haloalkylamines are highly specific against sympathomimetic substances or excitor sympathetic nerve effects and for example they will not block the pressor effects of hypertensin and pitressin (NICKERSON BULLOCK and NOMAGUCHI 1948 YOUMANS and RANKIN 1947) Antihistamine properties are however present in certain β haloalkylamines including dibenamine (NICKERSON 1949) and antagonism to the effects of serotonin on the bronchial muscle has been reported by BHATTACHARYA (1955)

BLOCKING ACTION

Circulating adrenaline and noradrenaline Block of the effects of these amines is the most prominent action of the β haloalkylamines As with all sympathomimetic blocking agents the effect on the vasoconstrictor action is the main property Reversal of the effect of adrenaline on the blood pressure is readily obtained The seemingly greater effect of a given dose of dibenyline on the pressor effect of adrenaline compared with noradrenaline is largely due to unmasking of the greater vasodilator component in adrenaline (NICKERSON *et al* 1953) A most important observation is that of GREEN *et al* (1954) who claimed that the vasodilator component of adrenaline and of noradrenaline demonstrated in the skin of the dog could also be blocked by an increased dose of dibenyline This is the only

active metabolite with cellular receptor sites is slow and open to competition

The nature of the reaction with cellular components has been studied *in vitro* (HARVEY and NICKERSON 1954) and reactions with sulphydryl amino and carboxyl groups were obtained The idea that alkylation of sulphydryl groups is the main reaction for adrenergic block (NICKERSON and GOODMAN 1948 NICKERSON and GUMP 1949) is nevertheless still in the hypothetical stage since *in vitro* active and inactive blocking substances were not clearly distinguished by their chemical reactions

BRODIE ARANOW and AXELROD (1954) suggested that another reason for the prolonged action might be the retention of the unchanged β haloalkylamine especially dibenyline in the body fat from which it was released slowly At high intravenous dose levels (23 mg/kg) they showed the presence of a substance with the same chemical reaction as dibenyline in the fat of a dog four days after administration Further using C^{14} dibenyline they were able to demonstrate radioactivity in the dog s plasma which ran parallel to the adrenaline reversing action for four days There has been no clear proof that the substance in the fat or the radioactivity in the plasma was unaltered dibenyline Using smaller oral doses of C^{14} dibenyline HOROWITZ and NICKERSON (1952) report that it did not appear to accumulate in fat even though an effective blockade was obtained

The obvious objection to all these experiments is that there is no proof that the substances measured by nonspecific physicochemical methods are not degradation products incapable of causing a block and therefore the experiments of HUNT (1949) are of particular importance He used two cats joined by cross circulation at varying times after administration of dibenamine to one and showed that a substance capable of causing adrenaline blockade was present in the circulation up to 4½ hours after administration The dose of dibenamine used was large (20 mg kg) However the time at which all blocking activity had disappeared was not investigated

The likely conclusions from this conflicting evidence are that while the β haloalkylamines may accumulate in fat with large doses it is not a necessary part of their blocking activity

METABOLIC FATE

Relatively little is known about the degradation of β haloalkyl amines *in vivo* BRODIE, ARONOW and AXELROD (1953) found no

unchanged dibenyline in the urine of dogs after intravenous administration and presented evidence that dealkylation with the formation of the corresponding amine was a major route of degradation

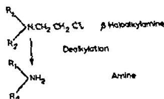


Fig 3

(Fig 3) The N phenoxyisopropyl N benzylamine was then rapidly broken down in other ways

SPECIFICITY

The β haloalkylamines are highly specific against sympathomimetic substances or excitor sympathetic nerve effects and for example they will not block the pressor effects of hypertensin and pitressin (NICKERSON BULLOCK and NOMAGUCHI 1948 YOUMANS and RANKIN 1947) Antihistamine properties are however present in certain β haloalkylamines including dibenamine (NICKERSON 1949) and antagonism to the effects of serotonin on the bronchial muscle has been reported by BHATTACHARYA (1955)

BLOCKING ACTION

Circulating adrenaline and noradrenaline Block of the effects of these amines is the most prominent action of the β haloalkylamines As with all sympathomimetic blocking agents the effect on the vasoconstrictor action is the main property Reversal of the effect of adrenaline on the blood pressure is readily obtained The seemingly greater effect of a given dose of dibenyline on the pressor effect of adrenaline compared with noradrenaline is largely due to unmasking of the greater vasodilator component in adrenaline (NICKERSON *et al* 1953) A most important observation is that of GREEN *et al* (1954) who claimed that the vasodilator component of adrenaline and of noradrenaline demonstrated in the skin of the dog could also be blocked by an increased dose of dibenyline This is the only

example of an inhibitory vascular effect of adrenaline and noradrenaline being blocked by any substance The high dose used, however may mean that this effect was nonspecific

Practical use of this blocking action on circulating adrenaline and noradrenaline has been made in patients with phaeochromocytoma where the blood pressure has been returned to normal levels and the typical attacks have been aborted (WALLACE and MCCRARY, 1955 BANNON and ALLEN, 1952)

Cardiac effects The β haloalkylamines do not block the stimulating actions of adrenaline on the heart so that in particular the method by which adrenaline causes increased force of cardiac contraction, which seems superficially analogous to vasoconstriction is almost certainly mediated by different means (NICKERSON and GOODMAN 1947 VLEESCHHOUWER 1947 HAIMOVICI and MEDINETS 1948 HECHT and ANDERSON 1947)

The β haloalkylamines are not without action on the heart however since the arrhythmias produced by intravenous injections of adrenaline can be reduced or prevented by their prior administration (WILBURNE *et al* 1947 HECHT and ANDERSON 1947)

Blocking of Sympathic Nerve Stimulation As with all sympathomimetic blocking compounds the β haloalkylamines are less effective for a given dose in blocking the effects of sympathetic nerve stimulation than in blocking circulating adrenaline and noradrenaline (NICKERSON and GOODMAN 1948)

The inhibition of reflex vasomotor effects does not seem to involve central nervous depressor action or autonomic ganglion block (FOLKOW and UVNAS 1948 NICKERSON and GOODMAN 1947)

The direct blocking action on blood vessels has been most clearly shown in the skin and muscle of the dog (GREEN 1953 GREEN *et al* 1954a b) The usual vasoconstriction in these sites following sympathetic stimulation was abolished completely by dibenyline given intravenously

The reflex vasomotor effects mediated by the sympathetic system are also largely blocked or inverted This applies to the effects of anoxia clamping the carotid arteries or cold (MARSH and VAN LIERE 1948 STONE *et al* 1948)

GENERAL CARDIOVASCULAR EFFECTS IN MAN

Administered by intravenous infusion or if active by mouth the β haloalkylamines usually cause postural hypotension, miosis and

vasodilatation most easily noted in the skin The postural hypotension leads to a reflex tachycardia (HECHT and ANDERSON 1947 HAIMOVICI *et al* 1948 1951 REDISCH *et al* 1952) Other effects are nasal congestion weakness and nausea or vomiting

The question of the site of action of the β haloalkylamines in man has been approached in another way DUFF (1956) has infused dibenyline intra arterially into the limbs of patients who had had a postganglionic sympathectomy performed The amounts were insufficient to produce a general systemic effect but vasodilatation occurred This indicates either a direct action on arteriolar smooth muscle or a blocking action on circulating adrenaline or nor adrenaline

EFFECTS ON THE KIDNEY

Because of the use of this drug in the treatment of hypertension the effects on the kidney may have a special interest In the dog whether anaesthetized or not reduction in blood pressure by β haloalkylamines was not accompanied by reduction in glomerular filtration rate or renal plasma flow which indicates a concomitant decrease in renal vascular resistance (MOYER and HANDLEY 1952) In conscious patients with hypertension dibenyline did not alter the usual fall in renal blood flow which follows the change from recumbent to erect posture (which is also present in patients with normal blood pressure) (FORD MOYER and SPURR 1953) In man therefore the renal vascular resistance does not seem to be markedly affected by dibenyline

CONCLUSION

The β haloalkylamines are seen to be most potent blocking agents for sympathomimetic effects and their actions seem to be almost entirely peripheral in the arterial wall Differences in the action on man compared with other animals may depend partly on the much smaller dose which is tolerated by man

REFERENCES

ANAN S (1929) *Jap J med Sci* (iv) 4 70
BANNAN W G and ALLEN E V (1952) *Proc Mayo Clin* 27 459
BHATTACHARYA B K (1955) *Arch int Pharmacodyn* 103 357
BOVET D SIMON A and DRUEY J (1937) *Arch int Pharmacodyn* 36 33
BRODIE B B ARONOW L and AXELROD J (1954) *J Pharmacol* 111 21

DUFF R S (1956) *Dibenyline Symposium Royal Society of Medicine London* 1956
FELLOWS E J McLEAN R A MACKO E KERWIN J F HALL G C MILNES F J WITT I H and ULLYOT G C (1954) *J Pharmacol* 110 463
FOLKOW B and UVNAS B (1948) *Acta Physiol Scand* 15 365
FORD R U MOYER J H and SPURR C L (1953) *Amer Heart J* 46 268
GREEN H O (1953) *Science* 118 570
GREEN H O MACLEOD J A ANDERSON D A and DENISON A B Jr (1954a) *J Pharmacol* 112 218
GREEN H O DENISON A B Jr WILLIAMS W O Jr GARVEY A H and TABOR C G (1954b) *J Pharmacol* 112 462
HAIMOVICI H and MEDIMETS H E (1948) *Proc Soc exp Biol N Y* 17 163
HAIMOVICI H MOSER M and KRAKAUER H (1951) *Proc Soc exp Biol N Y* 77 477
HALL G C MILNES F J WITTS I H and ULLYOT G E (1954) *J Pharmacol* 110 463
HARVEY S C and NICKERSON M (1953) *J Pharmacol* 109 328
HARVEY S C and NICKERSON M (1954) *J Pharmacol* 112 274
HECHT H H and ANDERSON R B (1947) *Amer J Med* 3 3
HOROWITZ R M and NICKERSON M (1954) *Fed Proc* 13 367
HUNT C C (1949) *J Pharmacol* 95 177
MARSH D F and VAN LIERE E J (1948) *J Pharmacol* 94 221
MENDEZ R (1928) *J Pharmacol* 32 451
MOYER J H and HANDLEY C A (1952) *J Pharmacol* 104 329
NICKERSON M (1949) *J Pharmacol* 95 27
NICKERSON M BULLOCK F and NOMAGUCHI G M (1948) *Proc Soc exp Biol N Y* 68 425
NICKERSON M and GOODMAN L S (1945) *Proc Amer Fed Clin Res* 2 109
NICKERSON M and GOODMAN L S (1947) *J Pharmacol* 89 167
NICKERSON M and GOODMAN L S (1948) *Fed Proc* 7 397
NICKERSON M and GUMP W S (1949) *J Pharmacol* 97 25
NICKERSON M HENRY J W and NOMAGUCHI G M (1953) *J Pharmacol* 107 300
REDISCH W TEXTER E C HOWARD R M STILLMAN P H and STEELE J M (1952) *Circulation* 6 352
STONE C A ACHENBACH P and LOEW E R (1948) *Fed Proc* 7 258
WALLACE L and McCRARY J D (1955) *J Amer med Ass* 157 1404
WILBURNE M KATZ L N RODBARD S and SURTSHIN A (1947) *J Pharmacol* 90 215
VLEESCHHOUWER G R DE (1947) *Proc Soc exp Biol N Y* 66 151
YOUMANS W B and RANKIN V M (1947) *Proc Soc exper Biol N Y* 66 241

GENERAL DISCUSSION

— —

DR A C DORNHORST (London) I should like to take up one point that Dr Peart mentioned concerning the sympatholytic effect of these drugs in contrast to their action by blocking circulating adrenaline The problem is at what dose level does this come in? I think it is quite clear that in man ordinary clinical doses have a sympatholytic effect This may be illustrated by their effect on the

reactive vasoconstriction which occurs after Valsalva s manoeuvre and is mediated through the sympathetic nervous system When a normal person carries out the Valsalva manoeuvre against a fixed pressure there is a decrease in the pulse pressure as a result of the diminished filling pressure of the heart This decrease in pulse pressure leads to peripheral vasoconstriction which is shown after the release of the pressure by an over shoot in arterial pressure to a level above the original base line If the same individual carries out Valsalva s manoeuvre two hours after 25 mg dibenyline there is a definite block of this over shoot There is virtually no reactive con striction and the blood pressure just quietly climbs back to normal thus demonstrating a sympatholytic effect

Dr Peart said that there seemed every reason to supppose that all the effects were entirely peripheral and that there were no central effects I am not so certain about this This dose level is very small compared with the doses apparently needed in animal preparations to block adrenergic nerve endings and I gath r from Dr Duff and Dr Ginsburg who have been doing some experiments with intra arterial dibenyline that at this dose level there is probably a very incomplete blockade We have some evidence of a central action although not of a vascular action Dibenyline has a certain reputation for the treatment of emotional hyperhidrosis—palmar sweating—and this appears to be well founded If you give a dose of 25 mg or so intravenously the palms do become dry This would be a very surprising effect for a pure adrenergic blocker since this is a purely cholinergic nerve pathway as far as is known and *in fact* intra arterial dibenyline in doses equivalent to about double that effective intravenously has no effect on palmar sweating at all This work which was done with Dr Andrew Herxheimer gives at least a strong hint that this drug has some central action and I am not at all certain that some of the sympatholytic effects may not be produced in a similar way

DR JEAN GINSBURG (London) Dr Duff and I have carried out some experiments with intra arterial chlorpromazine and dibenyline assessing the effects of these drugs on peripheral constrictor responses to adrenaline and noradrenaline in some 30 healthy subjects

When adrenaline was given intra arterially in a dose of 0 5 μg/min the blood flow in the hand fell from a resting level of about 10 ml/100 ml/min to about 2 ml i e to 20 per cent of the initial value After infusing chlorpromazine 1 2 mg into the brachial artery the hand flow increased to nearly 20 ml 100 ml/min double the initial value

When the same dose of adrenaline (0 5 μg/min) was then given, there was a reduction in flow which expressed in absolute terms was much the same as before (i e from 20 ml to 13 or 14 ml/100 ml/min) though the reduction was of course proportionately much less These results suggest that chlorpromazine does not completely block adrenergic activity

When the same experiments were repeated using noradrenaline instead of adrenaline the results were similar, except that after chlorpromazine the reduction in blood flow produced by noradrenaline was both absolutely and relatively less than before chlorpromazine had been given Statistical analysis of the figures obtained shows that in fact under these conditions in man chlorpromazine is more effective against noradrenaline than against adrenaline

We also gave dibenyline intra arterially using the same procedure and the same dose (1 2 mg) as with chlorpromazine There was again a considerable increase in blood flow to the infused hand in most of the subjects In this case however when the same dose of adrenaline (0 5 μg/min) was repeated there was practically no change in the flow showing that the action of adrenaline had been blocked by dibenyline both relatively and absolutely This inhibition of adrenergic activity was not determined by the increase in flow since in some subjects in whom there had been very little dilatation in the hand after dibenyline the constrictor response to adrenaline was blocked as effectively as in those in whom dilatation was much more marked Similar results were obtained with noradrenaline Dibenyline blocked the action of noradrenaline and adrenaline equally well and was far more effective in this respect than chlorpromazine

We were also interested to find that we could obtain these responses without delay and with doses as small as 1 mg/Kg body wt In animals effective adrenergic blockade has only been obtained after a latent period of several hours and with doses of 5–10 mg/Kg Whatever chemical transformation is undergone by dibenyline in the circulation must be very rapid We have been able to demonstrate dilatation in the hand and a reduction in the constrictor response to both adrenaline and noradrenaline within minutes if not seconds of infusing dibenyline into the brachial artery

DR N B CHAPMAN (Southampton) My colleagues and I in Southampton in association with Dr Graham in Cardiff have worked on the chemistry and pharmacology of some drugs which show anti adrenaline properties As to the formation of the ethyleniminonium

ion from the halogenoamines we have obtained what I think is quite good evidence

Firstly if you study a halogenoamine in which the halogen is very tightly bound in other words where fluorine is the halogen then there is no pharmacological activity to speak of There is no loss of halogen from the molecule and there is no formation of a thiosulphate consuming species in the system whatsoever

We have studied a series of compounds derived from the naphthyl methyl residue utilizing the halogens chlorine bromine and iodine The appropriate salts may be dissolved in an aqueous medium and one can liberate the base from the salt and then leave it to stand for a suitable period and extract from the aqueous medium with ether the unchanged halogenoamine and one is still left with a thiosulphate consuming species which one can determine One can plot a curve of the concentration of thiosulphate-consuming species against time which varies according to the compound one is working with often one gets 100 per cent conversion straight away

The question which arises is is this a three membered ring compound as was assumed by Nickerson in the first place and probably quite rightly or is it a different type of compound? One can study that by examining the formation of acidity *during the early* stages and during the whole of the reaction and if one studies that one find that with a compound which liberates the whole of its halogen immediately and gives a corresponding amount of ethyleniminium ion one gets scarcely any acidity at all initially

More recently we have in fact isolated analytically pure derivatives of the ethyleniminium ion as picrylsulphonates I wish I could say that the isolated picrylsulphonates consume all the thiosulphate that they ought to—but they do *not* But they do in fact consume 94 per cent of the required amount There are some things about the isolation of the ethyl *niminium* ion which we do not yet understand but for my part I do not think there is much doubt about the formation of the ethyleniminium ion from 2 halogenoethylamines which show antiadrenaline activity

DR D P GRAHAM (Cardiff) Dr Chapman has shown that it is possibl to take a compound such as SY 28 to prepare a solution of it and to estimate over a period of time the production and decay of what has been analytically proved to be ethyleniminium ion My part of the task was to take such *solutions* prepare them and remove any unaltered undecayed parent compound leaving a reasonably pure ethyleniminium ion solution and to assay biologically the

activity of such preparations against adrenaline noradrenaline histamine 5 HT, and so on

I had already published in 1953 with my colleague Dr Lewis, a study on three such compounds and have recently completed studies on five others, covering a wide range of such compounds and in every case we get within the limits of course of biological work a very close correlation between production of ethylenimonium ion and antinoradrenaline and antiadrenaline activity

The final definite proof that the intermediate product ethylenimonium ion is in fact the active species and responsible for the specific activity of this class of compound will, I hope, come very shortly because I now have in my hands as Dr Chapman has just told you a picrylsulphonate of a stable water soluble ethylenimonium ion For myself I feel quite sure that this will in fact prove to contain all the qualities of a wide range of these compounds

DR PEART I must apologise to Dr Chapman and Dr Graham for having overlooked their work I am very sorry about it but it does seem obvious then that the ethylenimonium ion despite my strictures must have more action than I believed it to have

THE VERATRUM ALKALOIDS

J G WIDDICOMBE

ALTHOUGH it is over 80 years since the pharmacology of the veratrum alkaloids was first investigated and their study since then has been extensive and fruitful we still do not know their mode of action in man This is because in experimental animals they cause hypotension and bradycardia by a number of mechanisms of which the most sensitive varies both with the species and with the particular veratrum extract or derivative used The only feature in common in these experiments is that small doses of the drugs act on the afferent side of visceral reflex arcs or on the central nervous system but have no effect on efferent nervous connections or on the blood vessels

If the concentration is great enough the veratrum alkaloids will stimulate or sensitize any excitable tissue for example they cause repetitive firing of isolated nerve and skeletal muscle fibres being potent depolarizing agents of the cell membrane However a minimal effective dose given intravenously causes hypotension and bradycardia as originally shown by BEZOLD and HIRT in 1867 These responses have been intensively investigated with veratrum extracts and with pure ester alkaloids such as protoveratrine cevadine and veratridine

BEZOLD and HIRT (1867) suggested that the cardiovascular response to veratrine was due to the stimulation of sensory receptors in the heart and this vagal reflex is usually called the Bezold reflex the Bezold–Jarisch effect or the coronary chemoreflex (DAWES and COMROE 1954) names which emphasize our ignorance of its physiological nature The fact that the hypotension and bradycardia are due to sensitization of vagal afferent end organs is established as follows The effects are abolished by cutting the vagi but since this procedure also interrupts the efferent cardioinhibitory fibres it would diminish the bradycardia from any nervous source However cooling the vagi to about 8°C abolishes the Bezold reflex although the cardiac efferent nerve fibres can conduct at this temperature (DAWES MOTT and WIDDICOMBE 1951a) In the innervated heart–lung preparation with separate circulation through the head and with only nervous connections between the thorax and head

veratridine elicits the Bezold reflex via the vagi when injected into the thoracic circulation but not from the cranial circulation unless larger doses are given (KRAYER WOOD and MONTES 1943) With regard to the hypotension this is abolished by cutting the vagi thus interrupting the afferent arc of the reflex the fall in blood pressure can be produced in the atropinized animal in which slowing of the heart is absent so that the hypotension is not entirely secondary to bradycardia The motor effects of the Bezold reflex include vaso dilatation in many parts of the body (DAWES *et al* 1951a DAWES and COMROE 1954)

The sensory receptors responsible for the reflex lie in the distribu tion of the coronary circulation since veratridine is effective when injected into the left ventricle but not when put into the ascending aorta (AVIADO, PONTIUS and SCHMIDT 1949) DAWES (1947) established that the ventricular muscle was the most sensitive site for obtaining a reflex response he cannulated branches of the coronary arteries of the dog (some going only to ventricular muscle) and the whole coronary arteries of the cat and showed that minute doses (0 5–1 μg) of veratridine injected into them caused a consider able fall in heart rate and blood pressure while the same quantities were ineffective elsewhere in the circulation There is thus no doubt that rapid intravenous injections of veratrum alkaloids in dogs and cats cause bradycardia and hypotension by sensitizing or stimulating afferent nervous structures in the ventricular muscle of the heart

There has been considerable speculation about the nature of the receptors sensitized by the veratrum alkaloids One view is that they are ventricular pressoreceptors whose function would be similar to that of the aortic arch and carotid sinus baroreceptors a buffer reflex limiting undue increase in left ventricular pressure There is evidence for such a reflex (DALY and VERNEY 1927) and activity from ventricular stretch receptor fibres has been recorded (WHITTERIDGE 1948 DICKINSON 1950) PAINTAL (1955b) has analysed the properties of these receptors and shown that they are sensitized by veratridine JARISCH and ZOTTERMAN (1948) have also recorded from cardiac afferent nerve fibres in the cat which responded to veratrine but their response to natural stimuli was not determined They discharged on pinching the ventricles and on occlusion of the aorta but these are drastic stimuli JARISCH suggested that the endings might play a part in such conditions as cardiac ischaemia In the dog activity in cardiac nerves from the left ventricle has been detected following intracoronary injections of veratridine but once again it was impossible to determine their

natural stimulus (DAWES and WIDDICOMBE 1953) Until single fibre preparations are obtained in the dog it will be difficult to establish what endings are excited by the veratrum alkaloids

Although it is the end organs for the Bezold reflex which are most sensitive to intravenous doses of the veratrum alkaloids in cat and dog there are other effects which may play a part in the hypo tension in man DAWES (1947) showed that small doses of veratridine sensitized a depressor reflex from the pulmonary circulation of the dog and similar reflex effects can be obtained in the cat with serum 5 hydroxytryptamine and certain amidines PAINTAL (1955a) has recorded nerve fibre activity from the lungs which was increased by the amidines and which he believes to come from the pulmonary vessels In addition it is known that veratrum can cause hypotension by a direct action on the central nervous system With rapid intra venous injections the threshold for this is higher than that for the Bezold reflex but with long la ting veratrum preparations or with infusions of pure alkaloids the central action may be as important as the reflex one at least in the dog (DAWES MOTT and WIDDI COMBE 1951b) This is especially seen with Veriloid one of the veratrum preparations in clinical use In the dog the action of this drug is only sometimes and partially abolished by cutting or cooling the vagi and part of its hypotensive action is therefore probably central However all the active alkaloids in Veriloid have not been determined and they probably differ from the pure ester alkaloids used for animal experiments In the cat Veriloid and veratridine infusions exert all their cardiovascular effects via the Bezold reflex The veratrum alkaloids can also sensitize baroreceptors in the carotid sinuses (AVIADO PONTIUS and SCHMIDT 1949) although the thres hold for this is higher than for the Bezold reflex at least as far as veratridine is concerned

It is clearly impossible to apply these results categorically to man Most of the therapeutic preparations are mixtures of alkaloids and the active ingredients may not be known we cannot be sure of their actions in humans from a knowledge of the specific effects of pure ester alkaloids in experimental animals But by analogy with animals it is probable that they work by sensitizing the Bezold reflex although a direct action on the central nervous system is also possible as indeed are actions on other reflex mechanisms It is not surprising that they cause toxic side effects such as nausea and vomiting but the fact that they seem to exert no effect on the motor side of cardio vascular reflexes so that postural reflexes are retained has been quoted in favour of their therapeutic use in hypertension

REFERENCES

AVIADO D M PONTIUS R G and SCHMIDT C F (1949) *J Pharmacol* 99 425
BEZOLD A VON and HIRT L (1867) *Unters physiol Lab Wurzburg* 1 73
DALY I DE B and VERNEY E B (1927) *J Physiol* 62 330
DAWES G S (1947) *J Pharmacol* 89 325
DAWES G S and COMROE J H Jr (1954) *Physiol Rev* 34 167
DAWES G S MOTT J C and WIDDICOMBE J G (1951a) *J Physiol* 115 258
DAWES G S MOTT J C and WIDDICOMBE J G (1951b) *Brit J Pharmacol* 6 675
DAWES G S and WIDDICOMBE J G (1953) *Brit J Pharmacol* 8 395
DICKINSON C J (1950) *J Physiol* 111, 399
KRAYER O WOOD E H and MONTES G (1943) *J Pharmacol* 79 215
JARISCH A and ZOTTERMAN Y (1948) *Acta physiol scand* 16 31
PAINTAL A S (1955a) *Quart J exp Physiol* 40 89
PAINTAL A S (1955b) *Quart J exp Physiol* 40 348
WHITTERIDGE D (1948) *J Physiol* 107 496

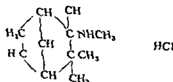
GENERAL DISCUSSION

PROFESSOR C HEYMANS (Ghent) I would like to draw attention to some important differences in pharmacological action between veratridine and protoveratrine at least in dogs In the dog, intravenous injection of veratridine causes a very mild bradycardia and fall in blood pressure After cutting the vagi there is no longer any bradycardia or hypotension Veratridine therefore acts via the Bezold reflex In the normal dog an intravenous injection of *protoveratrine also produces bradycardia and a fall in blood* pressure After cutting the vagi, injection of the same amount of protoveratrine does not induce bradycardia but there is still very marked hypotension But if in the same dog after cutting the vagi the carotid sinus nerves are also cut and the same amount of protoveratrine is injected intravenously no fall of blood pressure occurs Local applications of a fraction of a microgramme of protoveratrine in the carotid sinus area induces the same fall of blood pressure *so that we believe that protoveratrine does not act mainly* by means of the Bezold reflex but is active on the baroreceptor area After cutting the vagi and the carotid sinus nerves of the dog no amount of protoveratrine will induce a fall of blood pressure increasing doses induce a rise but never a fall in the level of blood pressure I think this is a very important and fundamental difference between protoveratrine and veratridine Therefore if we use mixtures of these substances the pharmacological action of the mixture will vary *depending on the proportions of these two important compounds* present

A POSSIBLE EXPLANATION FOR THE DEVELOPMENT OF 'TOLERANCE' TO GANGLION BLOCKING SUBSTANCES

ELEANOR ZAIMIS

In general all substances which interrupt transmission in autonomic ganglia may be referred to as ganglionic blocking substances. The various mechanisms by which such interruption is brought about have been exhaustively discussed during the last few years (MOE and FREYBURGER 1950; PATON and ZAIMIS 1952; PATON 1954; ZAIMIS 1955). Substances such as hexamethonium, pentolinium and azamethonium, which up to now have been extensively used clinically, produce an interruption of ganglionic transmission by competition with acetylcholine, a process which leaves preganglionic nerve endings and the ganglion cells unaffected. Qualitatively the actions of these three drugs are the same but they show slight quantitative variations, pentolinium, for example, being more active and longer lasting than the other two. None of these substances, however, is ideal and the search for a better ganglionic blocking substance still continues. Among newly discovered substances some appear quite interesting. Of these three—chlorisondamine dimethochloride (PLUMMER *et al.* 1955), 139C55 (ADAMSON *et al.* 1956) and mecamylamine (FORD *et al.* 1955; STONE *et al.* 1956)—are undergoing clinical trials and information about their actions both on animals and human beings is accumulating. Of these substances chlorisondamine dimethochloride and 139C55 are quaternary ammonium compounds but mecamylamine is not. It is a secondary amine and it is the first non quaternary ammonium compound to show such a powerful action at the ganglionic synapse. Quaternary ammonium



3 methylaminoisocamphane hydrochloride Mecamylamine or Inversine

compounds have the common drawback of being poorly and erratically absorbed when administered orally Mecamylamine being a secondary compound is easily absorbed and at first sight appears to be at a great advantage over the quaternary ammonium compounds But while this property is undoubtedly a great advantage from the

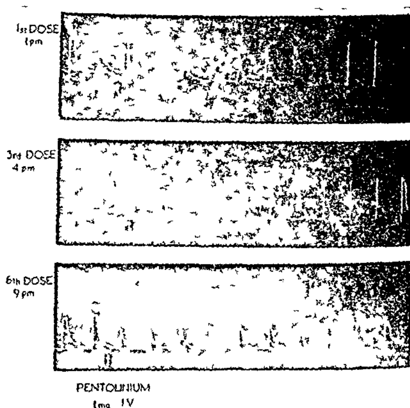


Fig 1 Cat (2 kg) Chloralose anaesthesia Contractions of nictitating membrane elicited every 3 minutes by preganglionic stimulation at a frequency of 10 shocks per second Period of stimulation 30 seconds

point of view of oral administration it may prove to be a disadvantage if the substance being a molecule which penetrates easily across the cell barrier of the choroid plexus has central nervous system effects

Another interesting point about these new ganglionic blocking substances is that the duration of action in all three is very prolonged With *chlorisondamine dimethochloride* especially experiments have been described in which the effects appear irreversible (PLUMMER *et*

al 1955) Such a prolonged duration of action makes one wonder whether their mode of action is the same as that of hexamethonium pentolinium or azamethonium which block ganglionic transmission by simple competition with acetylcholine or whether another process

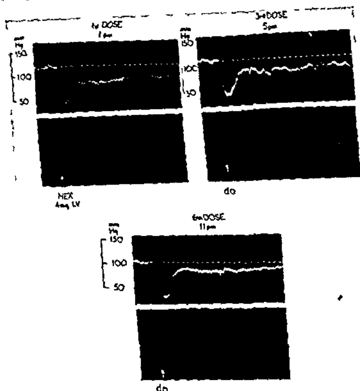


Fig 2 Cat (? 8 Kg) Chloralose anaesthesia Records of arterial blood *pressure* and contractions of nictitating *membrane* elicited every 3 minutes by pregang lionic stimulation at a frequency of 10 shocks per second Period of stimulation 0 seconds

is involved for instance interference with the release of the chemical transmitter or reduction of the sensitivity to acetylcholine of the ganglion cells Published work throws no light on this question the investigation of which is not only interesting but necessary There is no doubt that more experimental work and many clinical tests are required before their usefulness and safety can be fully estimated

compounds have the common drawback of being poorly and erratically absorbed when administered orally Mecamylamine being a secondary compound is easily absorbed and at first sight appears to be at a great advantage over the quaternary ammonium compounds But while this property is undoubtedly a great advantage from the

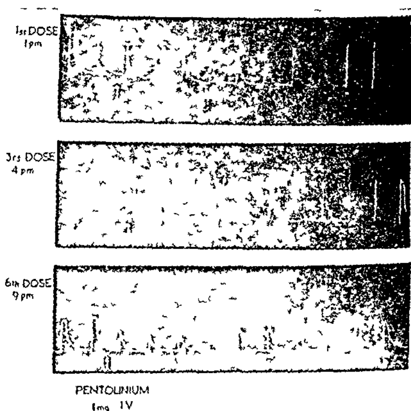


Fig 1 Cat (2 Kg) Chloralose anaesthesia Contractions of nictitating membrane elicited every 3 minutes by preganglionic stimulation at a frequency of 10 shocks per second Period of stimulation 30 seconds

point of view of oral administration it may prove to be a disadvantage if the substance being a molecule which penetrates easily across the cell barrier of the choroid plexus has central nervous system effects

Another interesting point about these new ganglionic blocking substances is that the duration of action in all three is very prolonged With *chlorisondamine dimethochloride* especially experiments have been described in which the effects appear irreversible (PLUMMER *et*

It has been the experience of all clinicians that a daily increase in the dose of a ganglionic blocking substance is necessary for the first few weeks if the initial rate of reduction in blood pressure is to be maintained. This is usually described as a decreasing sensitivity of the ganglionic synapse to the drugs or as tolerance development

There are however indications which suggest that this decreasing effect as far as blood pressure is concerned is not due to a decreased sensitivity of the ganglionic synapse to the action of these drugs Clinical observations show that parasympathetic ganglia do not develop tolerance to ganglionic blocking substances BRENDA



Fig 4 Cat (3 Kg) Chloralose anaesthesia. Contractions of nictitating membrane elicited by intra arterial injections of 3 µg of adrenaline before and after an intravenous injection of 3 mg of hexamethonium dibromide

MORRISON (1953) made a careful study of the parasympathetic effects in patients while they were developing tolerance of the blood pressure to hexamethonium and found that these effects increased in proportion to the dose given It seems improbable that only sympath tic and not parasympathetic ganglia should develop decreased sensitivity to the same substance Furthermore it is known that there is a remarkable difference in the speed at which this tolerance develops Some patients develop little tolerance and it is therefore possible to stabilise their dose within a week or ten days Others develop a very rapid tolerance which continues to increase for several weeks Thus development of tolerance shows no relation to the type of disease to initial severity of the disease or to the initial sensitivity of the patient to a test dose Again this lack of uniformity in the development of tolerance can hardly be attributed to a diminishing sensitivity of the ganglia to ganglionic blocking substances

From animal experiments on the other hand we know that under standard conditions ganglionic blocking substances of the hexamethonium type are extremely consistent in their behaviour and that the ganglionic synapse no matter what ganglionic pathway is tested

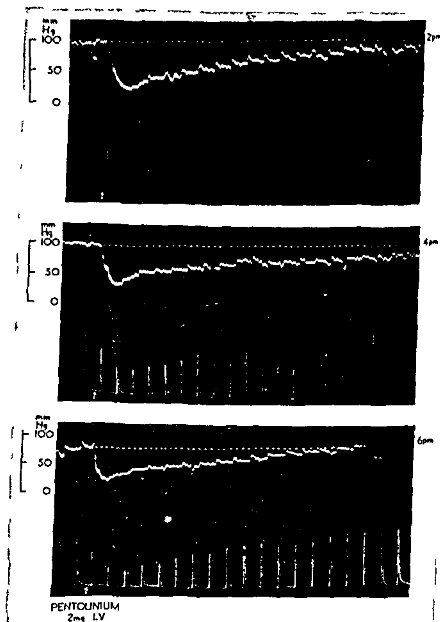


Fig 3 Cat (3 kg) Chloralose anaesthesia Records of arterial blood pressure and contractions of nictitating membrane elicited every 3 minutes by preganglionic stimulation at a frequency of 10 shocks per second Period of stimulation 30 seconds

All the e factors taken together suggested the possibility of a peripheral action of ganglionic blocking substances a sensitisation of effector cells to adrenaline and noradrenaline (ZAIMIS 1955) My colleagues Drs MANTEGAZZA and TYLER and myself have tested this possibility in a series of experiments and Figs 4 5 and 6 demonstrate some of the results so far obtained From these it is quite c ear that ganglionic blocking substances sensitise the effector

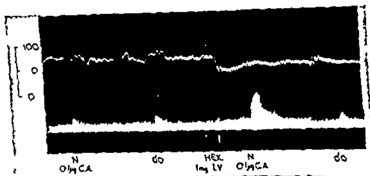


Fig 6 Cat (2 kg) Chloralose anaesthesia The poten iating effect of hexa methonium dibromide on vasoconstri tor responses produced by arterial injections of noradrenaline Record of arterial blood pressure (upper tracing) and venous outflow from a limb (lower tracing)

cells to adrenaline and noradrenaline This sensitisation though not great is always present and may very well mask the ganglionic effect In other words it appears possible that the reduced effect on blood pressure following on subsequent doses is due not to a diminishing sensitivity of the ganglionic synapse but to a sensitisation of the periphery to ad enaline and noradrenaline A steady effect on the blood pressure is therefore obtained when the ganglionic effect is great enough to counteract the peripheral sensitisation

That this decreasing response from the blood pressure is due to a peripheral action could be proved clinically by concomitant administration of an anti adrenaline substance This sounds easy enough in theory but there may be practical difficulties since none of the anti adrenaline substances known at present are powerful antagonisers of the intrinsically liberated sympathomimetic amines

REFERENCES

ADAMSON D W BILLINGHURST J W and GREEN A F (1956) In press
BARTORELLI C CARPI A and CAVALCA L (1954) *Brit J Pharmacol* 9 476

shows an increasing rather than a decreasing sensitivity to subsequent doses Fig 1 shows the result of an experiment on a cat in which contractions of the nictitating membrane were elicited by stimulation of the cervical sympathetic Three doses of pentolinium were administered at intervals of several hours and it is quite clear that both intensity of the block and duration of activity are increased

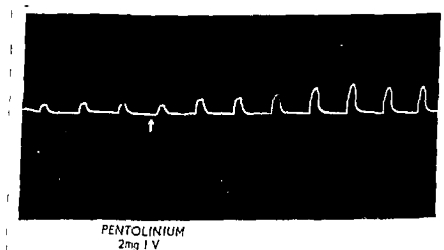


Fig 5 Cat (3 4 kg) Chloralose anaesthesia The effect of pentolinium bitartrate on the contractions of nictitating membrane elicited every 3 minutes by *submaximal post*ganglionic stimulation at a frequency of 10 shocks per second Period of stimulation 30 seconds

with subsequent doses But if in a similar experiment blood pressure is recorded at the same time then the increasing paralysis of the nictitating membrane by subsequent doses of a ganglionic blocking substance is always accompanied by a decreasing effect on the blood pressure Fig 2 shows this In this experiment repeated doses of hexamethonium were administered With subsequent doses there is a marked increase of the effect on the nictitating membrane but a *tendency of the blood pressure to return more rapidly to its initial level* Fig 3 shows the same result with pentolinium

Then there is the much discussed potentiation of adrenaline and noradrenaline which always occurs in the presence of a ganglionic blocking substance and which cannot be attributed only to the abolition of the normal compensatory nervous mechanisms as it is found both after vagotomy and after section of the spinal cord at a high level, (BARTORELLI *et al*, 1954)

doses of ganglion blocking agents do not produce complete ganglionic blockade tolerance could be due to increased activity of the un blocked vasoconstrictor pathways If this hypothesis is correct we should be able to restore the initial sensitivity to ganglion blocking agents in a tolerant patient if the still active pathways were partially blocked by an adrenergic blocking agent This hypothesis has been tested in an in patient clinical trial on eight patients *Pentolinium* was used as the ganglion blocking agent and dibenyline as the adrenergic blocking agent These drugs were given separately and in combination with suitable intervening rest periods in a fixed time schedule Our results have not yet been finally analysed but we have formed some strong provisional impressions Dibenyline does enhance the hypo tensive effect of pentolinium when the patient has become tolerant This effect however is much more marked when the patient is standing This marked postural hypotensive effect we appreciate does not necessarily prove or disprove our original hypothesis On the other hand we find that the hypotensive effect of this com bination is apparently much better maintained after discharge from hospital than other combinations we have tried perhaps due to this exaggerated postural effect Whether this combination of pentolinium and dibenyline will prove to be more effective than the more con ventional combinations in the treatment of hypertension we are not yet able to say

PROF BURN I was intrigued by Dr Zaimis observations on the increased peripheral effect of adrenaline after ganglion blocking agents Grant and Thompson have shown in the vessel of the rabbit s ear that the constrictor effect of adrenaline in the normally innervated vessels was relatively small but that if the ear was denervated the vessels became enormously more sensitive—about 1 000 times or even more—to the constrictor action of adrenaline injected into the artery They showed that this was due to or was accompanied by the disappearance of nonspecific cholinesterase and a substance which behaves like acetylcholine present within the vessel wall They put forward the conception that normally the vessel wall was being maintained in a state of vasodilatation by acetyl choline which was being formed continuously and that when adrenaline caused constriction it did so against the action of this acetylcholine I had therefore supposed that the increased sensitivity to adrenaline which is seen after hexamethonium might be because hexamethonium was blocking the acetylcholine mechanism in the vessel wall itself Dr Zaimis now upsets this because she shows that

FORD R DENNIS E and MOYER J H (1955) *J Lab and Clin Med* 46 815
MOE G K and FREYBURGER W A (1950) *Pharmacol Rev* 2 61
MORRISON B (1953) *Brit Med J* i 1291
PATON W D M and ZAIMIS E (1952) *Pharmacol Rev* 4 219
PATON W D M (1954) *Pharmacol Rev* 6 59
PLUMMER A J TRAPOLD J H SCHNEIDER J A MAXWELL R A and EARL A E (1955) *J Pharmacol Exper Therap* 115 172
STONE C A TORCHIANA M L NAVARRO A and BEYER K H (1956) In press
ZAIMIS E (1955) *J Pharm Pharmacol* 7, 497

GENERAL DISCUSSION

PROF HEYMANS Do all the ganglion blocking agents, including the most recently developed compounds in small doses block parasympathetic ganglia before they block the sympathetic? Is there any hope of finding a ganglion blocking agent, as Dr Ing suggested, which would be more specific in blocking sympathetic ganglia without interfering so much with parastmypathetic ganglia? The parasympathetic blocking action is one of the main troubles which limits their clinical usefulness

DR ZAIMIS None of the drugs at present known appears to be particularly effective in blocking sympathetic rather than parasympathetic ganglia The physiology of the two sets of ganglia is so similar that I am rather pessimistic as to the possibilty of *discovering* a substance which will paralyze either the parasympathetic or the sympathetic respectively without affecting the other

DR G KING (Stoke on Trent) Dr Stock and I at Stoke on Trent have been using an adrenergic blocking agent in an investigation into the mechanism of tolerance to ganglion blocking agents We were interested in the observation that this tolerance is specific to the hypotensive action of the drug We have objective evidence that this is true This observation suggests that in the hypertensive patient the blood pressure may be set at a higher level than normal and that when attempt is made to lower it by a ganglion blocking agent compensating mechanisms are brought into play which tend to revert the pressure to its initial raised level Such mechanisms might have a nervous or a humoral mode of action

We suggest as a possible nervous mechanism that since therapeutic

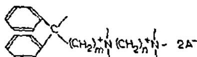
DISCUSSION PAPERS

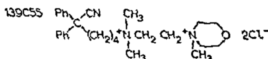
THE GANGLION BLOCKING ACTIONS OF THE DIQUATERNARY AMINO BENZHYDRYL NITRILES 356C54 AND 139C55

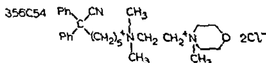
A F GREEN

A LARGE number of the benzhydryl compounds (I) referred to by Mr BILLINGHURST and others are powerful ganglion blocking agents Here I shall discuss the pharmacology of only two of these compounds namely the nitriles 356C54 and 139C55

(I)







Miss N B WARD and I have compared these compounds with pentolinium and Ecolid The mydriatic effect provides a convenient and fairly reliable measure of ganglion blocking activity in *many* but not all species Table 1 shows the doses increasing the pupil diameter to approximately two thirds of maximum under lighting conditions which were standard for each species but varied for different species 356C54 139C55 and Ecolid are very much more active than pentolinium in mice cats and monkeys These species

she also gets a potentiation of the action of adrenaline in the nictitating membrane Where the effects of adrenaline and acetylcholine are in the same direction as on the nictitating membrane I would have expected depression of the effect of adrenaline by hexamethonium

DR ZAIMIS I am sorry my findings do not confirm Professor Burn s expectations What is even more interesting is that ganglionic stimulant drugs such as tetramethylammonium and DMPP reduce the responses to adrenaline

carotid sinus reflex, elicited by clamping the common carotids, was also blocked or greatly impaired Within the same dose range contractions of the nictitating membrane caused in cats by prolonged preganglionic stimulation were inhibited but larger doses 0 3–1 0 mg/kg were necessary to block the effects of short bursts of stimuli applied infrequently to the cut nerve This difference appeared to be greater than that with hexamethonium or pentolinium (PATON 1951)

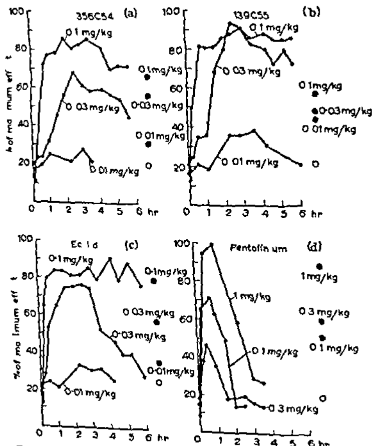


FIG. 1 The duration of mydriasis caused by subcutaneous doses of 356C54 139C55 Ecolid and pentolinium in cats The pupil diameters expressed as a percentage of those attainable with atropine are plotted against time in hours The circles open for the controls and filled for the treated groups represent the maximum observed degree of exposure of the nictitating membrane expressed as a percentage of that attainable with pentolinium Means for groups of four cats

have not shown great differences in sensitivity to these drugs but the mouse appears to be relatively less sensitive to pentolinium, and incidentally less sensitive to hexamethonium on intraperitoneal injection though not on intravenous injection The mydriatic doses of all these compounds in the rat are enormously greater than those in other species and the normal activity relationships do not hold

Table 1

The doses of 356C54 139C55 Ecolid and pentolinium increasing the pupil diameter of various species to approximately two-thirds maximal Each compound was tested at two or more dose levels in cats dogs and monkeys in groups of four and in mice and rats in groups of ten The clinically effective hypotensive doses in man are based largely on the experience of Dr S Lockett

Species	356C54	139C55	Ecolid	Pentolinium
	mg/kg	mg/kg	mg/kg	mg/kg
Mouse (i p)	0 06	0 06	0 1	2
Cat (s c)	0 03*	0 02*	0 025*	0 2*
Dog (s c)		0 05*		
Monkey (s c)	0 03	0 03	0 03	0 2
Rat (s c)	2	15	4	>50 (toxic)

* Nictitating membrane partly relaxed

Hypotensive dose mg/kg

Man (s c)	0 06–0 6	0 03–0 3	0 04–0 4	0 1–1·0

In the cat and the dog both parasympathetic and sympathetic systems are involved in the blocking effects since the mydriasis is accompanied by relaxation of the nictitating membrane

Comparison of the durations of mydriasis in cats (Fig 1) shows that the effects of these benzhydryl nitriles last very much longer than those of pentolinium and perhaps slightly longer than those of Ecolid the experiments also show that the onset of action of these benzhydryl compounds is relatively slow Similar differences occur in the rate of onset and duration of other characteristic ganglion blocking effects in various species including man

In anaesthetized cats and dogs doses of the benzhydryl compounds comparable with those dilating the pupil (0 03–0 3 mg/kg intravenously) generally lowered the blood pressure inhibited vagal bradycardia and reduced the hypertensive effect of DMPP, while increasing the hypertensive effect of the adrenalines In the dog the

As PATON indicated was the case for hexamethonium and pentolinium these experiments suggest that the degree of ganglion block caused by these drugs and especially by 139C55 depends to a large extent on the number of stimuli passing through the ganglion This may be related to the relatively slow onset of action of 139C55 and perhaps also to the observation that when postural syncope occurs in patients treated with this and analogous drugs it does not abruptly follow the assumption of the erect posture but comes on slowly This dependence of the degree of block on the amount of traffic through a ganglion could result in transmission in ganglia concerned with different functions being affected to different extents This explains why in the anaesthetized cat the nictitating membrane s response to short bursts of preganglionic stimulation of the cut nerve is affected less than a number of other functions It may also have some bearing on the observation (LOCKET 1956) that the doses of 139C55 and 356C54 which relieve clinical hypertension have not in contrast to the methonium drugs caused paralytic ileus

These benzhydryl nitriles like other ganglion blocking agents do however produce some effects on the alimentary tract In anaesthetized rats intravenous doses of 139C55 0 01-0 1 mg/kg lowered the blood pressure and comparable subcutaneous doses inhibited gastric secretion in Shay rats (0 03-0 3 mg/kg s c) and delayed gastric emptying in fasted rats (0 1-0 3 mg/kg s c) Since these drugs are not appreciably absorbed from the stomach the delay in gastric emptying can retard absorption When the drugs are introduced into the duodenum by injection in animals or by capsule in man the effects have been fairly uniform but as with other quaternary ammonium salts the effective dose has been about 10 times the subcutaneous dose

To sum up the benzhydryl compounds possess ganglion blocking properties resembling those of the methonium drugs They have the advantages of greater potency a slower onset and much longer duration of action The fact that their ganglion blocking effects seem more dependent on the degree of activity within the ganglion may be of importance in obtaining a greater degree of selectivity of effect and should be investigated further

REFERENCES

ADAMSON D W BILLINGHURST J W GREEN A F and LOCKET S (1956) *Nature London* 177 523
LOCKET S (1956) personal communication
PATON W D M (1951) *Brit Med J* 1, 773

Analogous observations have been made in mice where mydriasis developed more rapidly after an intravenous injection of either pentolinium or 139C55 if the mice were kept in the light than if the mice were kept in the dark There was however a difference between 139C55 and pentolinium in this respect (Fig 2) After 0 1 mg/kg 139C55, mice kept in the dark showed very little mydriasis within 5 minutes but if at this stage they were exposed to light their pupils rapidly dilated during the next 5 minutes or so After 1 mg/kg

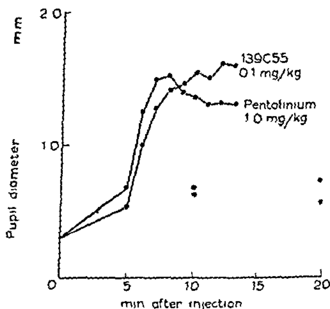


Fig 2 The effect of exposure to light on the mydriasis caused by intravenous doses of 139C55 and pentolinium in mice Continuous lines groups of 10 mice kept in the dark for 5 min and then exposed to light Dotted lines similar groups kept in the dark all the time except during measurement of the pupils

pentolinium rather more dilatation occurred in the 5 minute period in the dark and the rate of dilatation during the light exposure was more rapid When the pentolinium dose was increased to 2 mg/kg to give a duration of action more comparable with that of 0 1 mg/kg 139C55 the pupils dilated fairly rapidly even in the dark Similarly in dogs injected intravenously with 0 1 mg/kg 139C55 and kept alternately in dim and strong light for periods of 15 minutes to 1 hour the pupils paradoxically dilated in the strong light and returned to normal in the dim light—the change could be repeated several times in the same animal

The subjects were patients who had been admitted for the assess ment and treatment of hypertension and they were studied after they had been in hospital for at least a week and when the resting blood pressure had settled to a constant level All had normal renal function Each patient then received an intravenous injection of either 2–3 mg of reserpine or 2–3 ml saline all injections being given

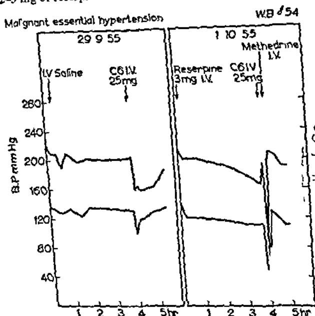


Fig 2 Male age 54 with malignant essential hypertension As Fig 1

slowly over a period of 5 minutes After this he remained in bed and the blood pressure was taken at half hourly intervals Between 3 and 4 hours later this time being chosen because it was felt that then the action of reserpine was likely to be at its height hexamethonium (usually 25 mg) was given intravenously At this time the patient was kept quite horizontal in order to avoid any postural hypotension The blood pressure was taken at frequent intervals after the injection of hexamethonium and the lowest level reached was recorded All blood pressure readings were taken by the same observer who remained ignorant of the nature of the original injection in each case

The whole procedure was then repeated after an interval of at least 24 hours with saline instead of reserpine or vice versa Some patients received reserpine first others the control injection

EFFECT OF RESERPINE ON THE HYPOTENSIVE ACTION OF HEXAMETHONIUM IN MAN

M HARINGTON

THERE have been reports from many centres of the treatment of hypertensive patients with a combination of one or more rauwolfia alkaloids and a ganglion blocking agent Clinical experience suggests that, at least in some cases, the addition of a rauwolfia alkaloid to the treatment of a patient who is already receiving a ganglion blocking drug enables the dose of the latter to be reduced, and side effects due to parasympathetic blockade correspondingly lessened, while still maintaining an adequate reduction in blood pressure In view of this finding the hypotensive action of single doses of these drugs has been investigated by administering them alone and in combination to patients under as controlled conditions as possible

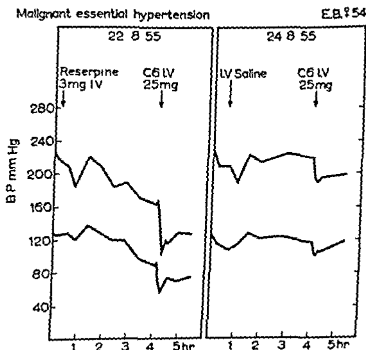


Fig 1 Female age 54 with malignant essential hypertension Intravenous hexamethonium has an increased effect when given after reserpine

3RD SESSION

(MORNING)

FRIDAY APRIL 6TH

Chairman Professor J McMichael

CLINICAL APPLICATIONS OF HYPOTENSIVE DRUGS

Examples of the results obtained are given in Figs 1 and 2 The averages of the results in 6 patients are shown in Table 1 The initial level of blood pressure was the same (within 10 mm) on both days of the test in each of these patients so that the figures obtained are comparable

Table 1

Effect of I V Hexamethonium and Reserpine on B P in hypertensive patients

	B P (mm Hg)	Fall (mm Hg)
A Initial level	209/121	
B *After C 6 alone*	*164/97*	45/24
C After reserpine alone	166/96	43/25
D After reserpine + C 6	107/64	102/57 (additional fall D-C = 59/32)

(All figures are mean of observations on 6 patients)

In all cases there was some fall in blood pressure after reserpine and Table 1 shows that this fall was under the conditions of these experiments of similar extent to that seen after hexamethonium alone (i e given after previous injection of saline) After the control injection no significant alteration in blood pressure was observed at the end of 4 hours in any case

When hexamethonium was given 4 hours after reserpine its hypotensive effect appeared to be increased This was the case in 4 out of 6 patients, in one of these the increase in effect was so marked that the patient collapsed and an injection of methedrine had to be given to restore the blood pressure (Fig 2) In the remaining two patients the diastolic pressure had already been reduced to normal levels (80 mm or less) by reserpine hexamethonium was then followed by a further fall but this was not significantly greater than with the latter drug given alone

Quantitative observations were not made on cardiovascular effects of the drugs other than on the blood pressure Flushing of the face and hands was uniformly seen after reserpine no obvious effect on this was noted after injection of hexamethonium

There is therefore no doubt that the hypotensive actions of reserpine and hexamethonium may be summated in hypertensive patients There is also some evidence that after reserpine the individual may become sensitized to the action of hexamethonium, though the site and mechanism of this effect remain obscure

RESULTS OF METHONIUM TREATMENT IN MALIGNANT HYPERTENSION (5-YEAR FOLLOW-UP)

J McMICHAEL

THE plan of this therapeutic trial was modified by two considerations

(1) The effects of a new remedy in a disorder so variable in its course as hypertension is most quickly judged by trial in the most acute and severe form (c f streptomycin which was established as an antituberculosis remedy in tuberculous meningitis)

(2) The results in the first few weeks showed pronounced amelioration of symptoms particularly restoration of sight in those who had been almost blinded by severe retinitis This and other symptomatic relief was so striking that an alternate case study would be unethical so our control cases had to be constructed from experience of malignant hypertension in the years before 1950 In the untreated series of 123 cases 90 per cent were dead in a year and 95 per cent in two years

MODE OF TREATMENT

The basis of treatment has been parenteral injection of ganglion blocking agents at 8 hour intervals in dosage adjusted to reduce the standing blood pressure to a nearly normal level Hexamethonium was used in the first instance but later patients were changed to pentolinium and dosage after the initial acute phase was past has been reduced to twice daily by means of a double night dose During the last year the addition of small daily doses of reserpine (usually ineffective by itself) has enabled us to get the same degree of blood pressure reduction with smaller and less troublesome doses of the ganglionic blocking agents Oral dosage has not been used because of irregularity of absorption and some early and distressing tragedies with oral hexamethonium

RESULTS

Malignant hypertension remains a grave disease as it is often too

failure may be arrested Various types of triple rhythm disappear and systolic murmurs vanish The heart size diminishes often dramatically Electrocardiographic manifestations of left ventricular hypertrophy change only very slowly Where angina pectoris is an accompaniment it may be relieved but drastic blood pressure reduction can induce anginal pain and even promote coronary thrombosis

KIDNEYS

There is no evidence that hypotensive treatment leads to deterioration of kidney function This is best illustrated by mentioning one patient who has had a blood urea round 100 mg per 100 ml through 5 years of treatment Pathological study shows that the fibrinoid necrosis in arterioles and glomeruli can undergo collagenization and healing

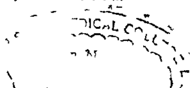
CEREBROVASCULAR COMPLICATIONS

Gross cerebral softening with residual paralysis is of course unaffected The risks of thrombosis and haemorrhage are still present in proportion to the severity of the anatomical vascular damage which has taken place in the brain before treatment was begun Transient cerebral ischaemic seizures may not recur with treatment but like angina they can also be precipitated by excessive pressure reduction

MODE OF DEATH

Most malignant hypertensives die a cardiorenal death with uraemia and heart failure playing equal parts A smaller number (20 per cent) die of cerebral haemorrhage These still account for deaths occurring under treatment but in addition dissecting aneurysms are becoming more frequent and 5 patients have developed a peculiar type of organizing oedema in the lungs In this manner drastic blood pressure reduction seems to alter the pathological consequences of the underlying disease

The total picture however is one of progress and we are quite certain that many patients are alive today in good health and working who would have died rapidly without treatment



far advanced in the degree of vascular damage to be amenable to therapy Many patients are admitted to hospital already dying of cerebral haemorrhage or advanced uraemia This continues to be the case even since 1951

Of 73 patients with malignant hypertension in the last five years 11 were regarded as untreatable for these reasons Treatment was begun in 62, but we now regard an initial blood urea significantly higher than 100 mg per 100 ml as hopeless unless some extrarenal factor like vomiting gastrointestinal haemorrhage or heart failure is contributing 10 of these 62 patients would be regarded as untreatable on our present day knowledge

Where the blood urea was initially under 60 mg per 100 ml (52 cases) the 5 year life expectancy is 50 per cent and even among the fatal cases life seems to have been prolonged Even when we start at this level of blood urea vascular damage and progressive nephritis or pyelonephritis may make the prognosis bad It should be remembered that pyelonephritis underlies malignant hypertension in 17 per cent of cases, and in patients under the age of 30 nephritis or pyelonephritis is the responsible factor in nearly every instance (25 out of 27)

EYE CHANGES

The disappearance of retinitis is the most dramatic event which follows blood pressure reduction Fresh haemorrhages and exudates vanish in a few weeks and although a little residual scarring may remain even this may shrink and the retina look quite normal in six months Papilloedema clears up in 2–10 months, but in one case it seemed to intensify before finally disappearing Retinitis has not recurred except in one patient who may possibly have had a subsequent thrombotic occlusion of a small branch of the retinal artery

HEADACHE

The intense crippling early morning headache is immediately greatly relieved but recurrence from time to time is always possible as a result of blood pressure fluctuations There seems to be a type of headache which occurs in the hypotensive phase if the pressure is too low

HEART

Gross and severe heart failure can vanish dramatically and even with imperfect b p control the progress of hypertensive cardiac

PRINCIPLES AND DETAILS OF HYPOTENSIVE THERAPY

F H SMIRK

I HAVE chosen the title *Principles and details of Hypotensive Therapy* because it has been our experience that it is necessary to be meticulous with detail in order to act in conformity with the principles

It is generally accepted that hypertension or the associated vasoconstriction leads to certain clinical manifestations If this is true it should be possible by blood pressure reduction to prevent the development of some clinical manifestations and to obtain recovery from some manifestations which have already developed Were this a simple relationship between hypertension and its clinical manifestations the object in treatment should be to reduce the blood pressure as near to normal as is practicable This is what we have tried to do except in certain instances In a few patients with cerebral arteriosclerosis a few with renal disease and in most patients with angina we have found it necessary to be content with smaller blood pressure falls and to adjust the extent of the blood pressure reduction to the requirements of the individual patient

Our results in general indicate that improvement in the clinical manifestations and in prognosis are closely related to the degree of control over the blood pressure level We try to keep the systolic blood pressure in the standing posture between 110 and 140 but the range is often between 85 and 160 systolic At these levels of the systolic pressure the diastolic pressure will be satisfactory

I should like to comment first on the extent to which important clinical manifestations can be relieved or prevented by adequate blood pres ure reduction

In our Dunedin series we have had 44 patients with malignant hypertension during the last six years who have either died or remained on treatment up to the present time We have 25 survivors and three out of eight of them have lasted between 5 and 6 years At 4 years we have 56 per cent survivors as against approximately 5 per cent in the KEITH–WAGENER series of untreated patients

Since a combination of a rauwolfia alkaloid and pentolinium became our standard treatment for advanced cases the mortality

the present time about 320 patients on treatment and have had 80 deaths in the last six years (25 per cent) We traced 57 out of 66 patients who stopped treatment Of the 57 26 had died a mortality of 45 per cent

PRINCIPLES OF TREATMENT

Space does not allow me to say much about the selection of patients except we treat all Grade IV and Grade III cases all cases with heart failure cardiac asthma or substantial breathlessness and all patients with repeated encephalopathic attacks Anginal patients with high blood pressures are given trial therapy as many of them get a degree of relief when the blood pressure is reduced judiciously Patients who have disabling symptoms are also treated Looking to the future I believe we now have evidence from the follow up of untreated cases that we are justified in offering treatment to symptomless patients as a preventive measure This would apply only to patients with high basal blood pressures—above 170 120 in females and above 150/110 in males Above these levels the mortality of untreated cases begins to rise steeply

The therapeutic regimes which we have relied on during the last six years may be divided into three periods first *hexamethonium* by injection second pentolinium and third pentolinium or other recently developed ganglion blocking agents in conjunction with rauwolfia alkaloids With the later methods we have had better control over the blood pressure and results have improved concurrently

There are a few important principles Unfortunately the observance of these principles involves a mass of detail which can only be hinted at in the space available but which in my view is essential for success The establishment of a good regime is a process in which a technique similar to that of bioassay is applied and at intervals reapplied to the individual patient

Factors influencing action of Ganglion blocking Drugs

The sympathetic nervous system plays a particularly important part in man probably because the adjustments which man has to make whenever there is a change from the sitting or recumbent to the standing posture are of a larger order than those which occur in the experimental animal In man modifications in homeostatic activity have a profound effect on the action of ganglion blocking drugs For example the response to ganglion blocking agents is

has been reduced further In the last 18 months the mortality in malignant hypertension cases has fallen to 11 per cent per annum This mortality is approximately halved when we eliminate the renal cases

Until recently our retinal Grade III cases did not do as well as the Grade IV cases This I attribute to the fact that we gave very much more attention to our malignant hypertension patients In malignant hypertension cases we were strict about adequate blood pressure reduction, even in the face of unpleasant side effects In Grade III cases we tended at first to forget about the grading once the exudative changes in the retina had disappeared This was a mistake I have no doubt now that Grade III cases remain more vulnerable even when all the clinical manifestations which distinguish them from Grade II cases have disappeared In the last 18 months we have paid more attention to our Grade III cases and our annual mortality has fallen to 9 9 per cent as against about 30 per cent in the KEITH–WAGENER series This includes renal deaths The mortality among Grade II cases has now fallen to 2 8 per cent per annum, as against about 7 per cent per annum in the series of KEITH and WAGENER

We consider that the results obtained provide a check on the efficiency of the methods used Congestive heart failure and cardiac asthma in severe hypertension are largely an expression of cardiac overload Therefore a majority of cases should clear up on blood pressure reduction alone Our experience is that on an adequate regime between two thirds and three quarters of a collection of cases of heart failure and cardiac asthma should clear without the use of ancillary measures such as digitalis mercurial diuretics, salt restriction or prolonged bed rest The degree of clinical improvement which occurs without using other measures is a guide to the efficiency of the hypotensive regime If the patient or the doctor gets careless with the regime the recurrence of breathlessness is an important reminder Furthermore if pneumonia or some severe infection causes recurrence of the congestive heart failure then digitalis mercurial diuretics and salt restriction are all available as reserves

In the retina all exudative changes—papilloedema retinal oedema hard and soft exudate and haemorrhages should either clear up or be very greatly diminished If more than an occasional case fails to improve considerably we feel that this represents an inadequacy of the regime used We think our results represent an improvement in the outlook of the Grade II III and IV cases we have treated We have at

remember that minor or occasionally major adjustments of dosage levels may be needed even after drug toleration is complete

We have found that adjustments in dosage have been greatly assisted especially now that there is a variety of drugs by stating for each ganglion blocking drug an initial dose and also an increment by which the dose may be varied. For example our initial oral dose of pentolinium is 20 mg and our increment is usually 20 mg occasionally 10 mg With mecamylamine we use an initial dose of 5 mg and an increment of 1 mg We give our patients instructions to raise the dose periodically by one increment at a time until there is a little faintness in the standing posture In the case of excessive action we ask them to reduce the dose by one increment at a time We find that if the dose is approximately one increment below the dose which produces a little faintness in the upright posture then in most cases the blood pressure during the trough of the blood pressure fall has dipped down to a near normal level We have used this method of controlling doses with five different ganglion blocking drugs alone and in combination with rauwolfia alkaloids It seems to be applicable to a number of drugs We check on our results by all-day tests conducted by technicians The extent to which these have been used in our clinic may be gauged by the fact that in the course of the last six years we have carried out over 16 000 all-day tests

Our standard treatment at the present time for severe cases is the combination of a rauwolfia alkaloid with a ganglion blocking agent The big advantage of the combination is that the dose of the ganglion blocker is decreased to two thirds or sometimes to a half of the original dose with consequent reduction in side effects We have used pure rauwolfia alkaloids in doses not exceeding 0 5 mg reserpine or 0 75 mg of rescinnamine or 1 mg of canescine per day On these doses we have had very little mental depression but this was a serious side effect when we were using larger doses

Canescine and rescinnamine are less likely to produce mental depression than reserpine In freedom from side effects canescine has been very satisfactory

The drugs Ecolid and mecamylamine are of considerable interest in that they are more active substances than pentolinium Moreover mecamylamine appears to be completely absorbed from the alimentary canal It may be anticipated that ileus induced by this secondary amine will be less dangerous than ileus induced by oral methonium compounds Some of our patients who were unable to take pentolinium effectively by mouth managed quite well with either Ecolid or mecamylamine On the other hand both these

increased by the vertical posture, loss of blood volume or of extra cellular fluid by venesection (300 ml) purgation mercurial diuresis and salt deprivation Also the action is increased during the splanchnic dilatation which follows meals during the hyperaemia of muscles after exercise with venous congestion of the legs after large doses of alcohol during application of negative pressure to the body surface after rauwolfia alkaloids after a major injury or surgical operation after fever and after the administration of pyrogens

The action of ganglion blocking drugs is decreased by infusions of blood or dextran solutions by raising the blood pressure with injections of noradrenaline angiotonin, or S methyl isothiourea and by the application of positive pressure to the external body surface

Almost all these actions can be explained in terms of the effects on sympathetic activity which they induce When homeostasis requires an increase in sympathetic nervous activity the hypotensive action of ganglionic blockade is increased When sympathetic nervous activity is decreased there is a corresponding decrease in the hypotensive action of ganglion blocking drugs

Knowledge of these actions enables appropriate adjustments of a régime to be made with improved control over the blood pressure level and decreased side effects

The Use of Posture

I think everyone agrees that when ganglion blocking agents are used it is necessary to take advantage of the standing or sitting posture in order to enhance the blood pressure falls We insist on our patients sitting propped up at night or failing this to raise the head of the bed on blocks 1 ft 4 in high In the more severe cases very large doses of ganglion blocking drugs may fail to reduce the blood pressure adequately if the patient lies flat

Meticulous adjustment of dose levels is required so as to reduce the blood pressure to about 120/80 *in the trough of the blood pressure fall With this is linked the allowances to be made for the development of drug toleration*

We have found that the dose of pentolinium by mouth requires to be adjusted to an accuracy of 10 or 20 mg Many patients who are on a good regime can appreciate the difference between the addition or subtraction of these amounts even when their oral dose is between 100 and 200 mg

The occurrence of drug toleration and the need to raise doses in order to keep pace with this, is well known It is also important to

that good results cannot be achieved by adopting a series of com promises with the principal objective

(5) There are few patients who need suffer much discomfort in order to get a good reduction in the blood pressure level But to obtain good blood pressure falls with few side effects regularly may require many clinical trials and modifications of the regime to suit the individual I think this needs the support of a specialized clinic with technical help and arrangements for adequate instruction supervision and follow up of patients

GENERAL DISCUSSION

PROFESSOR WILSON When ganglion blocking agents are pressed how long does it take before the side effects diminish and blood pressures can be approximated to the normal level? My experience which has been limited to severe cases of hypertension has been that there may be great difficulty in pushing the blood pressure in malignant hypertension to near normal Also does the lowering of blood pressure to the 140 level correspond to the actual trough level or is it a mean value?

PROF SMIRK My aim would be to produce such levels as 140 or 120 in the trough of the blood pressure fall with the patient standing It does seem that in malignant hypertension one has much more trouble with side effects than in most Grade III and certainly more than in Grade II cases with congestive heart failure or other severe manifestations and I would say that this applies particularly to the alimentary side effects I am sure that in the early stages one must not press too hard so that the side effects bring a patient to the point where he wants to abandon treatment However many of these patients become much more comfortable in the course of perhaps six or eight months We have had several malignant hypertension patients on treatment for four to six years and most of them are really comfortable now

I am quite confident that in many patients in the course of time there is a decrease in parasympathetic side effects even on the same

drugs induce sensations of vague malaise more frequently than pentolinium Mecamylamine is a more troublesome drug to handle and in the early stages of treatment, parasympathetic side effects are often more prominent Both drugs can also be combined effectively with rauwolfia alkaloids

The blood pressure is much less variable when a rauwolfia alkaloid is combined with the ganglion blocking agent In the past we found routine casual blood pressures at our outpatient clinic were very unsatisfactory for controlling the dose of ganglion blocking drugs when these were given alone but we have found casual blood pressures become quite useful when this combined form of therapy is employed

There appear to be individual differences between one drug and another in the sense that one patient may be definitely more comfortable on mecamylamine than on pentolinium and another patient more comfortable on pentolinium than on mecamylamine The same applies to reserpine, rescinnamine, and canescine I think there is scope for the use of several drugs and for making careful comparisons to see which suits an individual best

SUMMARY

(1) I think the object should be first to reduce the blood pressure and second to decrease side effects but without interfering with the blood-pressure reduction We fall short of our ideal but I think that every effort should be made to fulfil this objective

(2) I am unable to establish the validity of all the measures used in our clinic—the permutations and combinations would be too numerous—but they have in common the aim of returning the blood pressure to as near normal as we can get it We have very convincing evidence that our results in the last six years have improved considerably as we have made an approach towards this objective

(3) If we compare the mortality in our patients who were being treated by hexamethonium with the mortality on our present regime we find there has been a reduction from 26 to 9 9 per cent per annum in Grade III cases and from 12 to 2 6 per cent per annum in Grade II cases The results in Grade III and II represent in all 701 life years of experience with the treatments Dr VEALE finds that the difference in mortality in Grades III and II is significant at the levels of 1 in 100 and 1 in 50 respectively

(4) To be content with symptomatic relief is a disservice to the patients, who in severe cases are likely to die from a stroke We think

that good results cannot be achieved by adopting a series of compromises with the principal objective

(5) There are few patients who need suffer much discomfort in order to get a good reduction in the blood pressure level But to obtain good blood pressure falls with few side effects regularly may require many clinical trials and modifications of the regime to suit the individual I think this needs the support of a specialized clinic with technical help and arrangements for adequate instruction supervision and follow up of patients

GENERAL DISCUSSION

PROFESSOR WILSON When ganglion blocking agents are pressed how long does it take before the side effects diminish and blood pressures can be approximated to the normal level? My experience which has been limited to severe cases of hypertension has been that there may be great difficulty in pushing the blood pressure in malignant hypertension to near normal Also does the lowering of blood pressure to the 140 level correspond to the actual trough level or is it a mean value?

PROF SMIRK My aim would be to produce such levels as 140 or 120 in the trough of the blood pressure fall with the patient standing It does seem that in malignant hypertension one has much more trouble with side effects than in most Grade III and certainly more than in Grade II cases with congestive heart failure or other severe manifestations and I would say that this applies particularly to the alimentary side effects I am sure that in the early stages one must not press too hard so that the side effects bring a patient to the point where he wants to abandon treatment However many of these patients become much more comfortable in the course of perhaps six or eight months We have had several malignant hypertension patients on treatment for four to six years and most of them are really comfortable now

I am quite confident that in many patients in the course of time there is a decrease in parasympathetic side effects even on the same

ganglion blocking agent This is not invariable, and the reverse can happen One must also remember that there are several different Rauwolfia alkaloids and several effective ganglion blocking agents to choose from and a change from one to another may lead to a diminution in side effects

DR BYRON EVANS (Cardiff) Professor McMichael described a dramatic reduction in heart size as observed radiologically after treatment This picture is so unfamiliar to me that I would like to ask him what changes—if he had been able to have an autopsy before treatment and one after treatment—he would expect to find?

PROF MCMICHAEL I do not think hypertrophy regresses very rapidly but dilatation does The hearts would probably have been almost of equal weights but I think the capacity would be reduced Hypertrophy disappears very slowly The electrocardiographic signs of left ventricular hypertrophy remain although the heart size may have come down

DR W BRIGDEN (London) Have Professor McMichael or Professor Smirk met cardiac infarction or severe coronary insufficiency occurring at the trough of hypotension? Do the speakers consider that hypotension in general has any influence on the genesis of thrombosis in the coronary arteries or cardiac infarction and in particular in the acute hypotension caused by therapy?

PROF MCMICHAEL In patients who have had angina, gross blood pressure reduction can induce further angina and in two patients out of a total of about a hundred that we have had under treatment frank infarction has developed while the blood pressure was excessively low We have learnt from that experience to balance the pressure reduction at such a level that symptoms of that sort will not be induced but these arteriosclerotic complications present a very considerable problem

PROF SMIRK My experience is very similar In general if the blood pressure is reduced with discretion I do not think there is much risk of infarction angina is not infrequent and that is an indication to moderate the blood pressure reduction In a total of 460 patients we have had one patient who developed a definite coronary insufficiency as a result of excessive blood pressure reduction it was not fatal and electrocardiographic signs regressed I think the great safeguard is to control the blood pressure reduction by measurements made in the

standing posture, because then if the patient knows to lie down the blood pressure can always be raised promptly to a higher level We do not get worried about anginal attacks we tell the patient to lie down if an attack occurs

This problem is related to the question of whether cerebral thrombosis occurs when the blood pressure is low Our experience has been that cerebral thrombosis is a rare complication of blood pressure reduction provided hypotension i not induced under conditions which make it difficult for the patient to get the blood pressure up again In other words hypotension in the standing or sitting po ture is not dangerous if th patient knows when to lie down We know of one cerebral thrombosis in our series that developed as a result of excessive hypotension

DR LAWSON MCDONALD (London) Because of potential complications due to vascular disease in this form of therapy some two years ago it seemed reasonable in hypertensive patients with angina or a past history of thrombosis to place them on anti-coagulant therapy before commencing hypotensive therapy in order to mitigate the effect of sudden falls in blood pressure We have done this possibly with benefit and I would like to know if others have any experience of this supplement of hypotensive therapy

DR A R GILCHRIST (Edinburgh) There are three points I would like to raise in regard to treatment The first of these is in relation to acute left ventricular failure in the presence of malignant hypertension Traditionally these patients acutely distressed and dyspnoeic are treated with sedatives morphia and digitalis and so on I would like to ask Professor Smirk what his experience has been when those patients are treated with pentolinium only Does he feel justified in limiting the treatment entirely to intravenous pentolinium? Having done so successfully does Professor Smirk then continue with hypotensive drugs or does he then revert to digitalis in the hope of preventing further attacks?

The second point is in regard to the response which the patient with malignant hypertension who has a certain degree of renal damage will make I am sure that all of us who have used pentolinium in malignant hypertension are tremendously gratified with the amazing response which the majority of these patients make Yet there is a group in which the renal impairment has advanced to such a degree that the blood urea is a little on the high side and renal function is failing Schroeder and his co workers have made great

claims for the combination of hydralazine with a ganglion blocking drug and my own experience has been that using hydralazine in association with pentolinium takes some of these malignant cases over the hurdle, so to speak, the hydralazine is then stopped and pentolinium continued I would like to know if it is the experience of others that there is a borderland group with a raised blood urea in which hydralazine is a justifiable combination with pentolinium

Thirdly, when the patient is frankly uraemic does it not appear that giving pentolinium makes a bad situation worse? Does not a reduction of pressure aggravate the situation very considerably? It appears that the therapeutic response in malignant hypertension is largely determined by the degree of renal damage Experience with pentolinium suggests that early renal damage is reversible there is a further stage just on the borderland where pentolinium combined with hydralazine may be occasionally helpful and there is a final stage where a reduction of blood pressure aggravates the situation significantly

Prof Smirk I believe that the treatment of the acute attack of cardiac asthma when the patient comes in with gross breathlessness is one of the most dramatic demonstrations of the effect of this type of therapy By intravenous injection of a ganglion blocking agent in fractional doses—this is just the one situation where we prefer hexamethonium to pentolinium because of its shorter duration of action—the acute decrease of the cardiac overload may relieve breathlessness within a matter of one and a half minutes without any other measures whatsoever We always try these drugs first alone and in cardiac asthma it is seldom that any other measure such as sedation or digitalis is required If we cannot get a result within fifteen or twenty minutes we would use other measures but usually the attack is over within five minutes or less

In hypertensive congestive heart failure it is also our practice not to use digitalis mersalyl or a salt free regime unless we get an inadequate improvement on the ganglion blocking agents alone because thereby we discover whether the hypotensive regime is adequate or not The object is to reduce the cardiac overload and we prefer to see the effect of this before using other measures

Renal cases of malignant hypertension constitute one of the most awkward of all problems I think many of us feel we are not helping significantly with the treatment of renal disease though we may retard deterioration But we can treat the hypertension which accompanies renal disease If the blood urea is raised as a result of

heart failure occurring concurrently then I believe by improving the circulation something can be gained I agree that some advanced renal cases are made worse by treatment but I believe they deserve trial therapy with repeated estimations of the non protein nitrogen in the blood If additional nitrogen retention is occurring one must allow the blood pressure to return to a higher level

I have had little practical experience with hydralazine which is generally believed—I think on good evidence—to increase the renal circulation I have been prejudiced against it because we had so many side effects in the early stages and made our patients uncomfortable

PROF McMICHAEL I agree with Professor Smirk I found that patients asked to go back on hexamethonium when they were put on hydralazine Hexamethonium is very uncomfortable and if hydralazine was worse than that it must have been really bad Dr Hood who has much experience with this drug perhaps has another opinion

DR HOOD We have tried it in about four hundred cases together with other agents We have used a combined regime in about five hundred cases altogether and about four hundred are under continuous treatment I entirely agree with Professor McMichael that hydralazine used as a single agent is exceptionally unpleasant and is of no value whatsoever But with the combined regime we can achieve a little more blood pressure reduction in the severe and malignant cases than by using only rauwolfia and a ganglionic blocker In a severe renal case with a marked rise in non protein nitrogen we would give a small dose of reserpine start with very small closely-spaced doses of pentolinium and then very rapidly increase the hydralazine it is in this type of case and only in this type that we go up to enormous levels of hydralazine and it is a striking fact that this particular type of case will easily tolerate doses up to 800 900 or 1 000 milligrams daily In a case with advanced renal insufficiency we usually get during the first weeks a further increase in non protein nitrogen and in serum creatinine we adjust the blood pressure reduction carefully according to the results of the laboratory tests We have perhaps been able to reverse two or three cases with renal function slightly more impaired than those described by Sokolow and Schottstaedt but we have never been able to get a complete reversal of the malignant syndrome and an improvement in renal function in cases which have had an initial renal insufficiency as low as to be expressed by an endogenous creatinine clearance

below 30 litres/24 hr or a little more than 20ml/min It has been easy to normalize within a few weeks non protein nitrogens as high as 90 mg per cent, if other factors such as congestive failure, dehydration, or an acute exacerbation of pyelonephritis played a dominant role in creating renal insufficiency and have been brought under control

HYPOTENSIVE DRUGS CLINICAL EVALUATION UNDER CONTROLLED CONDITIONS

GEORGE A PERERA

THE arterial blood pressure is unique in the number of variable factors which can influence its quantitative determination Among these factors are the position and relaxation of the subject his state of mind and the circumference of his upper arm not to mention the mood and countenance of the examiner It is noteworthy that repeated contacts between physician and patient are apt to exert a neutralizing effect on extraneous pressor *stimuli* with the result that blood pressure values decline in the early weeks of casual study more often than they rise Yet with surprising unawareness of the magnitude of these response many therapists attribute their success solely to the action of an assortment of hypotensive drugs

Since I find it difficult to evaluate the experience of others I shall present only my own—a series of limited observations by a single investigator in a particular setting The hypotensive drugs were studied both in the hospital and clinic The former offered excellent controlled conditions The drugs were administered singly rather than in combination and their action was appraised not only by the effects apparent during their use but also by the reversal of these effects after their withdrawal Observations on ambulatory subjects were conducted in an out patient clinic to which they returned at weekly intervals

The following drugs will be considered in this report the rauwolfia alkaloids which act primarily on the central nervous system the veratrum alkaloids and hydralazine with their more complex action directed towards the cardiovascular system and the hexamethonium compounds and pentolinium as examples of drugs which are potent blockers of synaptic transmission in autonomic ganglia

The rauwolfia alkaloids in addition to bradycardia and tranquilizing effects may provoke serious mental depression rarely postural hypotension and very rarely oedema even to the point of

below 30 litres/24 hr or a little more than 20ml/min It has been easy to normalize within a few weeks non protein nitrogens as high as 90 mg per cent if other factors, such as congestive failure, dehydration, or an acute exacerbation of pyelonephritis played a dominant role in creating renal insufficiency and have been brought under control

HYPOTENSIVE DRUGS CLINICAL EVALUATION UNDER CONTROLLED CONDITIONS

GEORGE A PERERA

THE arterial blood pressure is unique in the number of variable factors which can influence its quantitative determination Among these factors are the position and relaxation of the subject his state of mind and the circumference of his upper arm not to mention the mood and countenance of the examiner It is noteworthy that repeated contacts between physician and patient are apt to exert a neutralizing effect on extraneous pressor stimuli with the result that blood pressure values decline in the early weeks of casual study more often than they rise Yet with surprising unawareness of the magnitude of these responses many therapists attribute their success solely to the action of an assortment of hypotensive drugs

Since I find it difficult to evaluate the experience of others I shall present only my own—a series of limited observations by a single investigator in a particular setting The hypotensive drugs were studied both in the hospital and clinic The former offered excellent controlled conditions The drugs were administered singly rather than in combination and their action was appraised not only by the effects apparent during their use but also by the reversal of these effects after their withdrawal Observations on ambulatory subjects were conducted in an out patient clinic to which they returned at weekly intervals

The following drugs will be considered in this report the rauwolfia alkaloids which act primarily on the central nervous system the veratrum alkaloids and hydralazine with their more complex action directed towards the cardiovascular system and the hexamethonium compounds and pentolinium as examples of drugs which are potent blockers of synaptic transmission in autonomic ganglia

The rauwolfia alkaloids in addition to bradycardia and tranquilizing effects may provoke serious mental depression rarely postural hypotension and very rarely oedema even to the point of

congestive failure (PERERA, 1955) We have determined recently that serotonin (5 hydroxytryptamine) may give rise to sodium retention and the electrolyte changes following rauwolfia administration may be related to this activity The many side effects of hydralazine are well known despite reported calculations that it increases cardiac output without impairment of coronary flow or myocardial nutrition, we have been impressed by the apparent number of patients who developed cardiac pain or showed an increased frequency of anginal attacks while receiving the drug The usefulness of the ganglionic blockers is limited somewhat by tolerance, postural hypotension the concomitant effects of parasympathetic blockade the need for close observation or self regulation and the development of rebound phenomena upon withdrawal It is now reasonably clear that the ganglionic blockers lower the blood pressure through a decrease in cardiac output rather than through modification of peripheral resistance They appear to affect a significant redistribution of blood to the splanchnic bed

The following conditions were employed in all patients studied in the hospital All subjects had documented primary (essential) hypertension and were without evidence of cardiac cerebral retinal or renal involvement In most instances a baseline period of at least three weeks in the hospital preceded the administration of the drugs The sodium content of the diet was maintained at more or *less constant levels and* was not restricted *Each drug was tested in* at least 10 patients Casual measurements of blood pressure were recorded daily and in addition the blood pressure was taken by me each morning with the subject lying quietly in bed the lowest systolic and lowest diastolic of five successive readings being recorded Only those patients whose resting blood pressures remained in excess of 140/90 at the end of the baseline period were included in the study Finally in those instances in which a hypotensive response took place so regarded for our present purposes when the resting diastolic blood pressure fell 10 or more mm of mercury the validity of the observation was supported by witnessing a rise on withdrawing the drug usually by replacing it with a placebo

EVALUATION IN THE UNCOMPLICATED PHASE OF PRIMARY HYPERTENSION

The *rauwolfia* alkaloids (reserpine 0 25 mg b i d or Raudixin[R] 50–100 mg b i d) administered for periods of at least three weeks in the hospital, produced a depressor effect in *4 of 10 patients*

Experience with ambulatory subjects in the uncomplicated phase and treated for at least one month yielded similar results Thus when given to 30 such patients the rauwolfia alkaloids appeared to result in a lower casually recorded blood pressure in 17 but in 6 of these doubt may be cast on the depressor action inasmuch as the blood pressure failed to rise again on withdrawing the drug for one month It should be mentioned at this point that all those in whom a response to rauwolfia was observed either in the hospital or ambulatory were clearly tense hyperkinetic and emotionally labile patients usually with tachycardia

No *veratrum* derivative whether given orally or parenterally was associated with a decline in the blood pressure of hospital patients until dosages reached levels which gave rise to nausea or vomiting Furthermore only two of 10 patients given small doses of a veratrum viride preparation on an ambulatory basis showed a dramatic fall in arterial tension—which was then sustained at low levels by a placebo

Hydrala ine (beginning with 25 mg t i d by mouth and increas ing until an effect was produced or until the daily dosage reached 750 mg) modified the blood pressure in 4 of 12 hospital patients and only to a small extent even though therapy was maintained for at least one month In no instance in the 5 ambulatory patients tested with hydralazine in doses reaching 500 mg per day was there a significant change in the casual blood pressure

Although the initial effective dose varied considerably both parenteral *hexamethonium* and oral *pentolinium* lowered the recumbent resting blood pressure in all but one of 20 hospital patients treated with each drug and reduced the standing blood pressure of all

Our experience concerning the use of these agents in uncomplicated hypertension can be summarized briefly as follows The rauwolfia alkaloids in either crude or purified form give sedative benefit to some restless and anxious patients We have seen no benefit from any veratrum compound and no longer do we believe that hydrala zine is effective when used without other drugs Until more has been learned of the potency and associated reactions of the ganglionic blockers it would seem wise to exclude them from use in an asympto matic period of a disease with such a long average duration As long as we remain ignorant of basic mechanisms and without proof that we have inhibited the advance of disease the use of hypotensive drugs in this phase has only experimental value and little therapeutic justification

EVALUATION IN THE ACCELERATED (MALIGNANT) PHASE OF PRIMARY HYPERTENSION

A crude rauwolfia preparation (Raudixin[R] 100 mg b i d) was administered to 10 hospital patients in the accelerated phase for 2–4 weeks without effect on either the clinical state or the blood pressure (Perera, 1954) In a larger survey of ambulatory patients this drug has been seldom of value in this stage, either alone or in combination with other drugs

In 30 hospital patients in the accelerated phase—without congestive failure, but with proteinuria, some degree of nitrogen retention and retinopathy with papilloedema—*pentolinium* lowered the blood pressure to normal or near normal This was frequently associated with regression of the eyeground changes, but renal insufficiency was not improved Only a small percentage of this group could be maintained adequately following discharge from the hospital More extensive trials were conducted in patients with various complications and with earlier stages of the accelerated phase It will suffice to say that our experience supports the view that such ganglion blocking agents as pentolinium lower the blood pressure relieve symptoms improve severe retinopathy and help congestive failure more consistently than can be achieved by rest sedation, and routine hospital care However in our hands these drugs failed to modify azotemia—providing congestive failure was not contributing—beyond the fluctuations one might see without specific treatment In fact at times blood pressure reduction decreased renal blood flow with adverse effects on the nitrogen retention Side effects and difficulties of regulation have kept us from using the ganglionic blockers successfully in other than cooperative patients with advanced disease Only rarely have we observed that *hydralazine* has produced convincing additive action

In the accelerated phase we are dealing in most instances with a progressive condition which leads rapidly to death If attendant symptoms can be relieved if unpleasant manifestations can be improved or if life can be prolonged in a state in which it is worth living then strong measures would seem justified

* * * *

There is no doubt that hypotensive drugs are useful in the management of some patients with primary hypertension but their use calls for thorough familiarity with the agent in question and with the individual patient I feel sure I will not be contradicted if I say that

hypotensive drugs may give rise to symptomatic improvement and may modify some of the manifestations and complications of the disease—but these results do not take place consistently I doubt furthermore that anyone can construe the results as being curative rather than suppressive What of the effect of therapy on the prolongation of life? It seems to me that insufficient time has elapsed to permit anyone to make valid statements about drugs employed at other stages than the accelerated phase In that phase however providing renal damage is not advanced the lives of some patients have surely been lengthened by the ganglionic blockers (PERERA 1956)

Certain investigators believe that reduction in blood pressure by such drugs as pentolinium can alter the evolution of the accelerated phase Others declare that the accelerated phase has been eliminated when retinopathy and papilloedema are present no longer These attitudes discourage inquiry and are inconsistent with all the facts It is possible that blood pressure reduction is dependent on the influence of these drugs upon the autonomic nervous system and that an entirely different mechanism may be involved in the beneficial results This point of view can be illustrated best by well known facts concerning papilloedema in hypertensive states To regard it simply as the product of a marked elevation of diastolic blood pressure leaves unexplained the higher incidence in younger males rather than older generally female patients its appearance after the blood pressure has been lowered by other means the rare spontaneous amelioration without a fall in arterial tension and while renal damage is becoming progressively more severe It may not be a justified assumption that retinal pathology represents necrotizing arteriolitis for retinopathy and papilloedema may be found in patients with phaeochromocytoma—in the absence of any sign of renal dysfunction and with no pathological evidence of the accelerated phase We must await further confirmation through serial renal biopsies and other devices Although one cannot exclude the possibility that drugs achieve their benefit via the hypotension they produce such an hypothesis is far from validated

I should like to add a final word of summary and prediction Hypotensive drugs have brought us new and useful means to relieve symptoms to help manifestations and sometimes to prolong life There are no data as yet to indicate that drug therapy is specific or will solve the basic problems of primary hypertension Most investigators believe that an unknown humoral factor is responsible for the arteriolar constriction of this disorder superimposed upon which

are variable neurogenic influences If such be the case, drugs which block neurogenic centres or peripheral ganglia should not prove curative and their advantages will probably not exceed those of sympathectomy

REFERENCES

PERERA G A (1954) *Proc Soc Exp Biol* 86 453
PERERA G A (1955) *J Amer med Ass* 159, 439
PERERA G A (1956) *Circulation* 13 321

DISCUSSION PAPERS

TREATMENT OF ESSENTIAL HYPERTENSION WITH HYPOTENSIVE DRUGS

C BARTORELLI

I SHOULD like to give a short account of the results of treatment of arterial hypertension with some of the more recent antihypertensive drugs

All the patients considered were suffering from essential hyper tension they were treated some in their homes others at hospital The drugs used were hexamethonium reserpine and Ecolid given either singly or in combination

HEXAMETHONIUM

Starting in December 1951 hexamethonium has been administered to 67 patients entirely by the oral route The dose has averaged 0 5–2 0 g hexamethonium ion daily (usually in the form of the bitartrate) The duration of treatment was from a few weeks up to 2 years 8 months

Of these 67 patients 12 have died 6 of cerebral haemorrhage 4 of renal failure 1 of myocardial infarction and 1 of dissecting aortic aneurysm In 23 treatment was stopped because of failure of co operation 8 have been treated with other drugs 10 had to stop treatment because of side-effects and in 9 the treatment was ineffective

Our results can be summarized as follows

Excellent	8 (12 %)
Satisfactory	16 (24 %)
Mediocre	17 (25 %)
Unsatisfactory	26 (39 %)

The difficulties of treatment with hexamethonium are well known and I have referred to them previously (BARTORELLI 1953) Our

clinical results suggest that there are only very limited indications for the oral administration of hexamethonium salts particularly if *prolonged treatment with this drug alone is contemplated* The great number of side effects and the impossibility of obtaining consistently low blood pressure readings throughout the 24 hours make this an impracticable form of treatment, especially outside hospital practice

RESERPINE

From October 1953 50 subjects have been treated with reserpine The average dose has been 1–3 mg daily Of these 50 patients 2 have died from uraemia 5 have received other treatment and in 17 treatment has been stopped because *of failure of co operation*

The results are summarized as follows

Excellent	12 (24%)
Satisfactory	14 (28%)
Mediocre	9 (18%)
Unsatisfactory	15 (30%)

Of all the drugs available for the treatment of hypertension reserpine is certainly one of the easiest to use on account of its low toxicity In the dosage employed treatment has never had to be *stopped because of side effects When diarrhoea has occurred* this has disappeared on reducing the dose However its hypotensive action is not very marked and varies considerably from one case to another

If the action of reserpine is predominantly on the central nervous system at the level of the hypothalamus as reported by most authors we might presume that its effect would be most marked in cases where there is an important neurogenic component to the hypertension However as this is almost impossible to establish clinically in individual cases one can only be guided by the practical results of treatment

COMBINATION OF RESERPINE AND HEXAMETHONIUM

At the symposium on ganglionic blocking agents held at Milan in 1954 I drew attention to the advantages of combining reserpine with hexamethonium It was observed that when this combination of drugs was given by mouth it was possible to reduce the effective

dose of hexamethonium this had the advantage of avoiding some of the gastrointestinal effects since on the one hand the dose of the ganglion blocker is smaller and on the other the action of reserpine on intestinal motility counteracts the effect of hexamethonium

Twenty one patients received reserpine 1–2 mg and hexamethonium 0 5–1 0 g daily Of these 21 1 has died of renal failure in 5 treatment has been stopped owing to lack of co operation and in 2 it has been stopped because of lack of any effect

The results are as follows

Excellent	9 (43%)
Satisfactory	3 (14%)
Mediocre	4 (19%)
Unsatisfactory	5 (24%)

There is no doubt that this combination or others which are under trial will allow the use of ganglion blocking drugs in treatment with a wider margin of safety than has been possible hitherto

ECOLID (SU 3088)

This drug has been given intramuscularly to 14 hypertensives and orally to 8 A dose of 2 5–5 mg intramuscularly produced a fall in blood pressure in every case in the upright posture but was effective in only a few while recumbent Characteristics of the drug are its long duration of action (12–14 hours) and a postural effect which is often more marked than with other ganglion blocking drugs With the doses used fainting in the upright position has been observed up to six hours after administration of the drug A considerable fall in blood pressure may occur on standing even after 24 hours at a time when the lying blood pressure has returned to its normal level

With oral administration the usual doses have been 25–100 mg The longest duration of treatment has been *one* month With this dosage the hypotensive effect has not been adequate in the recumbent position but the fall of blood pressure which has always occurred on standing has *not* been disabling Side effects observed have included dryness of the mouth difficulty in accommodation weakness and constipation

Our results demonstrate that the action of Ecolid is prolonged particularly as regards postural hypotension We cannot yet make a definite statement as to its practicability as a form of treatment

clinical results suggest that there are only very limited indications for the oral administration of hexamethonium salts particularly if prolonged treatment with this drug alone is contemplated The great number of side effects and the impossibility of obtaining consistently low blood pressure readings throughout the 24 hours make this an impracticable form of treatment especially outside hospital practice

RESERPINE

From October 1953 50 subjects have been treated with reserpine The average dose has been 1–3 mg daily Of these 50 patients 2 have died from uraemia, 5 have received other treatment and in 17 treatment has been stopped because of failure of co operation

The results are summarized as follows

Excellent	12 (24%)
Satisfactory	14 (28%)
Mediocre	9 (18%)
Unsatisfactory	15 (30%)

Of all the drugs available for the treatment of hypertension reserpine is certainly one of the easiest to use on account of its low toxicity In the dosage employed treatment has never had to be stopped because of side effects When diarrhoea has occurred this has disappeared on reducing the dose However its hypotensive action is not very marked and varies considerably from one case to another

If the action of reserpine is predominantly on the central nervous system at the level of the hypothalamus as reported by most authors we might presume that its effect would be most marked in cases where there is an important neurogenic component to the hypertension However as this is almost impossible to establish clinically in individual cases one can only be guided by the practical results of treatment

COMBINATION OF RESERPINE AND HEXAMETHONIUM

At the symposium on ganglionic blocking agents held at Milan in 1954, I drew attention to the advantages of combining reserpine with hexamethonium It was observed that when this combination of drugs was given by mouth it was possible to reduce the effective

THE ACTION OF ECOLID ON VASOMOTOR TONE IN THE LIMBS

Our attention was particularly attracted by the marked postural fall in blood pressure in hypertensives treated with the ganglion blocking drug Ecolid In certain subjects and with certain doses the hypotensive action of the drug was only manifest in the standing position while in other cases this action was so drastic as to make treatment impracticable

With the aim of analysing the mechanism of this well marked postural effect the changes occurring in vascular resistance in the limbs have been calculated, in 8 patients receiving 2 5-5 mg Ecolid by intramuscular injection from the variations in blood flow observed in the limbs by means of a modification of the plethysmo graphic method of GOETZ In order to convert the observed value for the blood flow into the absolute value a correction must be applied at the same time it is necessary to know the exact volume of the digit under observation, a measurement which is never very accurate If however differences in blood flow are considered only in relation to the initial level there is no need to introduce this correcting factor (wh ch GOETZ and other authors make equal to 3) It is possible to calculate with sufficient accuracy the slope of the curve starting at the time of venous occlusion and for the duration of one pulse beat (Fig 1) The blood flow is then proportional to the tangent of the angle of slope of this curve If the value of this tangent in basal conditions is made equal to 100 it is easy to calculate the successive variations in this measurement and hence in blood flow

The changes in vascular resistance in the toes and in the distal phalanges of the index fingers were calculated from the alteration in arm blood pressure as compared to the resting level and from the alteration in blood flow in the regions under consideration If these variables as measured under resting conditions are given the value 100 then any change in one or other variable will alter the ratio between them This ratio which has the value 1 under basal con ditions is an expression in arbitrary units of the state of the vascular resistance in the limbs

Since fluctuations in the mean arterial pressure are thought to be transmitted similarly to different parts of the body at least in the larger arteries such as the brachial or femoral any differences in blood flow observed must necessarily reflect alterations in the vascular resistance

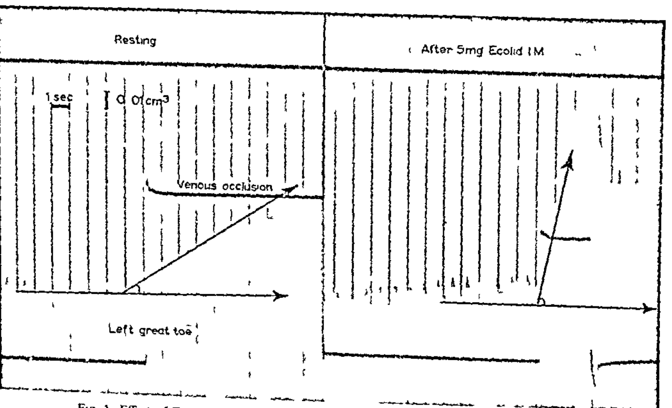


Fig 1 Effect of Ecolid on blood flow in the great toe The flow is markedly increased

After administration of Ecolid the difference between the vascular responses in the upper and lower limbs is so marked that it is obvious without resort to the calculations described above (Figs 1 a d 2) It can be seen that after Ecolid the curve of toe volume rises much more steeply whereas that of finger volume is unchanged or is even flatter

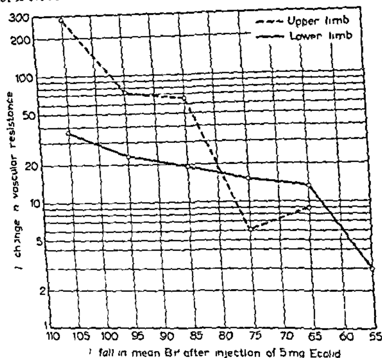


Fig 3 Decrease in blood flow to limbs plotted against fall in blood pressure produced by Ecolid in hyperten ive patients For description see text

Our results are summarized in Fig 3 in which the change in vascular resistance as a percentage of the resting value is plotted against the fall in mean blood pressure also expressed as a percentage of the initial level In this diagram the observations have been grouped according to variations of 10 per cent in the blood pressure It is clear that the decrease in vascular resistance is much greater in the lower limbs than in the upper in those cases where the blood pressure measured in the recumbent position at different times after intramuscular injection of Ecolid had not varied significantly from

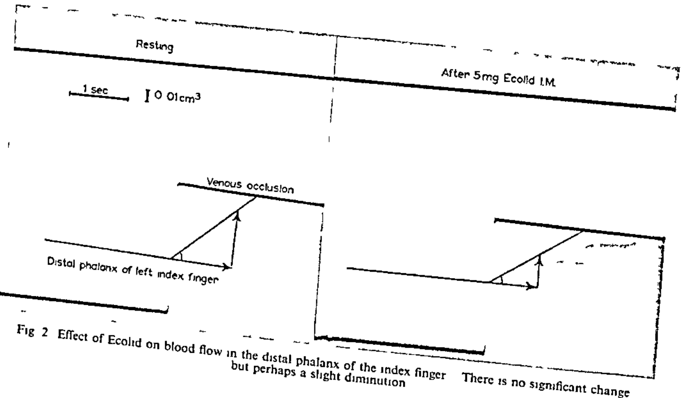


Fig 2 Effect of Ecolid on blood flow in the distal phalanx of the index finger There is no significant change but perhaps a slight diminution

FIVE AND A HALF YEARS EXPERIENCE OF COMBINATIONS OF HYPOTENSIVE DRUGS MAIN PRESENT DIFFICULTIES

B HOOD

IN a joint programme from two medical departments we have tried the newer hypotensive agents during the last 5½ years in more than 500 cases of hypertensive disease Our general aim has been to reach the best possible reduction of blood pressure with a minimum of side effects using any combination of drugs and way of administration Thus we have not been engaged in a clinicopharmacological study of a single agent at a time On the whole we have made an approach intermediate between those of SMIRK (1954) and SCHROEDER (1954) although a little closer to the latter After the start in 1950 with oral hexamethonium as the single agent we have successively added hydralazine rauwolfia and veratrum to a flexible system adapted not only to the severity but also to the degree of cooperation possible in the individual case The improvement in the possibilities of treatment has been striking and the chief problem has gradually switched from formidable side effects to how to find the level of B P that might be safe in the presence of advanced vascular disease

Some years ago we tried to make a retrospective survey of our results from the medical department where our study started Fig 1 shows that about 20 per cent of the patients were admitted in their terminal complication and died usually in a few days One third was considered to have too advanced vascular disease (massive cerebro vascular lesion advanced general cerebral deterioration fresh myocardial infarction marked rise in N P N) for treatment We were able to try the newer hypotensive agents only in about 20 per cent of the total population under 65 years About 11 per cent of this population remained under continuous treatment at the end of the three year period These were all improved but the figures were on the whole disappointing As is seen in Fig 2 the picture has during 1954 and 1955 improved radically We have extended the attempts of active treatment both to the groups of too advanced and too mild hypertension Also a good number of the cases from the first

its initial value When the fall in blood pressure is more marked, the vascular resistance in both regions studied decreases similarly and may reach a value of less than one tenth of the original resistance This considerable reduction in vascular resistance in the limbs and the fact that it takes place principally in the lower limbs, may provide at least a partial explanation of the marked postural effect of Ecolid

GENERAL CONSIDERATIONS

It will have been noted that a considerable number of our patients have stopped treatment on account of failure to co operate and this has been independent of whether treatment has been easy to control or has been effective This is a very important problem It is difficult to get useful results without close co operation between patient and doctor particularly in the early stages of treatment when the dosage has to be adjusted to the individual case The hypertensive must be persuaded to regard his hypotensive treatment in the same light as the diabetic his insulin Too often the hypertensive patient has a dangerous sense of well being when his pressure is high while when the pressure is lowered by treatment his capacity for work is impaired For this reason the degree of lowering of the blood pressure achieved by hypotensive drugs is not necessarily the best criterion of the efficiency of treatment In fact we do not attempt to reduce a grossly elevated pressure to physiological levels as is done by some workers, if this is done, an individual whose circulation has been accustomed to an elevated pressure over a long period of time may have difficulty in adapting himself to a level of arterial pressure which although physiological is much lower than that which had ensured an adequate blood supply to vital organs hitherto The aim of treatment should in our opinion, be to avoid any sudden rises in pressure such as commonly occur in hypertensive patients and may have serious consequences This can be done if the blood pressure is maintained so far as is possible at the basal level—that is to say the level observed in the patient at rest and after several days in bed a level which we establish for each individual patient It is nevertheless possible in some younger patients with hypertension of recent onset and in the benign phase to achieve levels of pressure that are near the normal

(Professor Bartorelli gave his communication in French)

REFERENCES

BARTORELLI C and RUMOLO R (1953) *Clin Terap* 5 3
BARTORELLI C (1953) *Journées Thérap* Paris G Doin
BARTORELLI C (1954) *Atti Soc Lombarda Sci Med Biol* 9 433

period of investigation The hypotensive agents have been tried in 64 cases We have somewhat arbitrarily divided these into two groups one adequately and the other inadequately treated To the

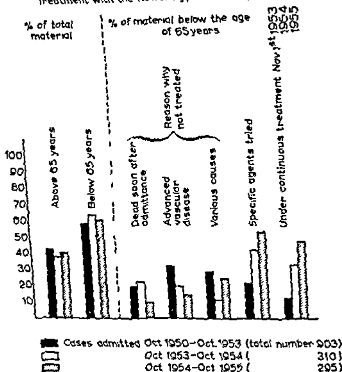


Fig 2

inadequately treated group we have referred cases where the treatment was given up at least *one* month before death (mainly our own early cases treated with oral hexamethonium) and those which have been treated in the three medical departments outside our own area of activity and thus have not been handled according to the principles which rapidly developed after the introduction of parenteral hexamethonium

The patients considered to have had the best treatment obtainab

three year period, where treatment had been abandoned due to side effects have been brought under control These cases do not appear in Fig 2

We have thought that the time is not yet ripe for a definite analysis of the results in benign hypertension In this group of more than

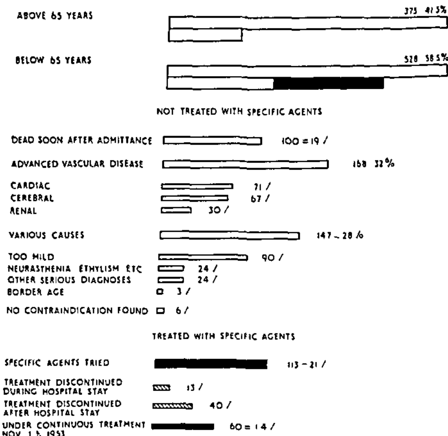


Fig 1

400 patients we have had 6 deaths two of which were unrelated to the hypertensive disease

Six months ago we made a survey of our results in Grades IV and III Fig 3 shows the findings in cases with papilloedema For purposes of comparison we collected material from 5 Swedish medical departments between the years 1945–1954 The total comprises 178 cases *Of the 87 cases treated with older methods only 3 were alive* and of them two were in a very bad condition at the end of the

as follows We start with a single dose of reserpine (0 5 mg or less) a day Then pentolinium is started in 5 oral doses a day (parenteral pentolinium is reserved for cases with renal insufficiency encephalo pathy or those developing severe constipation or meteorism on oral administration) The dosage is increased until side effects occur and these are thoroughly discussed with the patient A small cut in

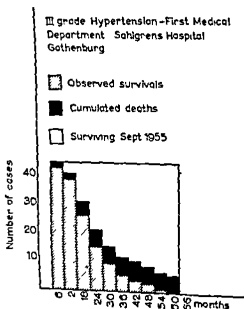


Fig 4

dosage is made and then hydralazine is introduced and advanced to 300–500 mg per day Only in very exceptional instances have we given more than 500 mg hydralazine per day

After the individual components of the treatment have been carefully adjusted for half a year or more a mixed pill has in a number of cases been composed of the drugs two pills being given five times a day Table 1 summarizes the results and causes of death in adequately treated cases of Grades IV and III

The two deaths registered as due to hypotension—? myocardial infarction—occurred in bed during sleep Both are considered to have lived longer and more comfortable lives with the treatment than they would have done without On the other hand we have had

at the time have been referred to the adequately treated group To begin with some of the early cases were given parenteral hexa methonium but have later been transferred to a combined regimen Among the patients in this group are 5 with advanced cerebral

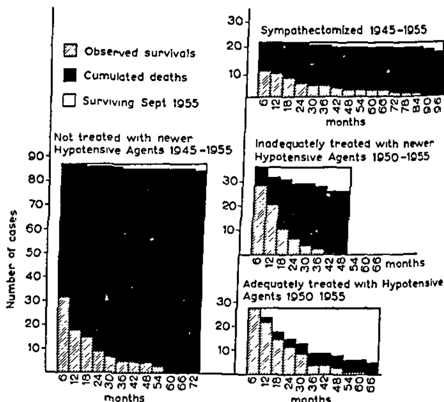


Fig 3

deterioration 6 with nonprotein nitrogen between 50 and 90 mg per cent and 2 with advanced congestive failure

Fig 4 shows the survival in hypertension Grade III For rather obvious reasons material collected for comparison from several departments might be very misleading in this group and we have therefore only given the data on the patients treated with the newer hypotensive agents

In Grades IV and III as well as in the most severe of the benign variety the programme of treatment has gradually been worked out

nonuraemic malignant hypertension than in the big group of severe and longstanding cases of the benign variety

We have never been able to accomplish a complete reversal of the malignant syndrome in the presence of reduced renal function when the endogenous creatinine clearance is below 30 litres per 24 hours which would correspond to a filtration of about 20 ml per minute It has however been fairly easy to normalize a raised N P N (highest figure 89 mg per cent) particularly where factors as vomiting and dehydration due to encephalopathy congestive failure or exacerbation of chronic pyelonephritis might be assumed to play a role

Our main difficulties at the present time may be summarized as follows

No combination of elaborate methods including E C G during graduated and increased work load vector electrocardiography and cholesterol determinations seem to give us accurate enough information about the state of the coronary vessels to know what to expect when the blood pressure is reduced particularly in the elderly A detailed clinical history and a very cautious system of trial and error seems to be the best way when the problem is to reduce the blood pressure in hypertensives with angina pectoris as the dominant symptom

A few of the patients in Grades IV and III are still referred to us so late that their renal function is at or below the critical level It should be possible to improve on the early diagnosis of retinopathy and renal insufficiency Blood N P N determination is too insensitive Serum creatinine is better

There is the forever present question—when and with what should the early or the moderate case be treated?

As for late toxicity I only want to mention the fact that in about 400 patients treated with hydralazine we have only seen the fully developed lupus erythematosus like syndrome once a butterfly exanthema once some ten cases with mild articular symptoms two cases with moderate thrombocytopenia and in the early days two cases of reactivation of chronic polyarthritis lasting for several months Only very seldom have we used doses above 400 mg a day

REFERENCES

SCHROEDER H A (1954) *Amer J Med* 17 540
SMIRK F H (1954) *Brit Med J* 1 717

three deaths similar to those SMIRK has described in fairly well controlled patients where a lapse in treatment led to a sharp blood pressure rise and a cerebral catastrophe

Since this series was completed 8 further cases with papilloedema have come under my personal control In the whole series of 31, 21 patients are either strictly normotensive or only on isolated occasions exhibit diastolic pressures as high as 110 mm

Table 1

Hypertension Grades IV and III, adequately treated

Living	IV	III
Full work	16	21
Able to work	4	10
Unable to work	3	1
Complete reversal eyegrounds	18	27
Azotaemic—Improved renal function—under treatment	6	—
Total Number of patients	23	32
Dead	**IV**	**III**
Encephalomalacia	1	—
Cerebral haemorrhage	—	2
Cerebral oedema	—	1
Hypotension—?myocardial infarction	2	—
Organized fibrinous pulmonary oedema —Doniach	1	—
Suicide	1	—
Uraemia—congestive failure (Cortical adenoma—pyelonephritis)	—	1
Unknown	—	1
Cancer of the pancreas	—	1
Total number of dead	5	6

This is a striking fact a result like this can in our experience not be reached with a combination of rauwolfia and ganglionic blocker We agree with SCHROEDER that the mechanism of action of hydralazine in these cases is worthy of thorough investigation On the whole the establishment of normotension in the malignant hypertensive human does not seem to have aroused such great interest or basic research as partly successful procedures have done in the renal hypertensive dog

As to blood pressure reduction our results are in fact, better in

days of 1950 were full of reports of disasters occurring from the oral use of hexamethonium its irregularity of absorption made its oral use extremely dangerous Since we went systematically on to sub cutaneous injection we have had little trouble with severe side effects such as intestinal paralysis That was the major cause of disaster The bowel became paralysed tablets which had previously been taken were still lying about in the bowel and hexamethonium poisoning sometimes went on for days on end Patients often died in uraemia and one of our patients became practically decerebrated That sort of experience practically brought this whole therapeutic business into complete disrepute I would like to hear Professor Smirk s views on the oral use of pentolinium

PROF SMIRK We did not use oral hexamethonium except on an experimental basis at the beginning We were strongly opposed to the routine use of oral hexamethonium because of the side effects to which Professor McMichael has referred and all our early work was done on parenteral therapy When pentolinium came along we found we were able to handle a large proportion of patients by oral th rapy but some patients still had so many side effects that we had to revert to injections When later we used rauwolfia alkaloids so as to diminish the effective dose of pentolinium we found that a large majority of patients could be managed using oral therapy and in our experience very much more comfortably and with fewer side effects than by injection So we have gone over almost entirely—not completely we still have a few on injection—to oral therapy

PROF BURN How is it that pentolinium can be given orally but not hexamethonium?

DR M HARINGTO I We have made a few studies of the excretion of pentolinium in the urine after oral administration The drug is excreted quantitatively in the urine after parenteral injection so that its excretion can be taken as a measure of absorption We have found that as with hexamethonium the absorption of pentolinium after oral dosage is both poor—only 5–10 per cent is absorbed—and in some cases irregular In the same patient absorption may vary as much as tenfold from one day to another In view of this possibility of irregular absorption we still tend to stick to parenteral administra tion in our cases although many people have reported more con sistent results with oral *pentolinium* This applies particularly where there is evidence of failure of renal function

GENERAL DISCUSSION

DR S LOCKET (Romford) I should like to refer to some clinical experience with the recently developed ganglion blocking drugs 356C54 and 139C55, whose chemistry and pharmacology have been described by Billinghurst and Green During the past two years we have tried these drugs out in some 60 cases of severe hypertension As with other ganglion blocking agents we have found oral administration too variable in its results and for the purposes of this trial they have always been given by injection The blood pressure has been measured with the patient sitting in a chair, as this is normally the way in which the patient has it taken by the doctor in his surgery

The type of result we have obtained has been as follows Taking 100 mm diastolic pressure as a maximum desirable level, with 5 mg 139C55 we may get five and a half hours of hypotension, while in the same patient with 15 mg we may get twenty hours below this arbitrary level It seems that increasing the dose not only increases the intensity but also the duration of hypotensive action and this relationship may be greater than linear at these critical doses

We have given the same dose of drug to the same patient at repeated intervals over a fortnight and observed no change in the hypotensive response, in other cases some adjustment has been necessary during the first few days, but as a whole with this group of drugs given by injection tolerance does not seem to be a marked feature and the dose remains relatively constant after the first three weeks

Comparing in the same patient the different drugs given in the same dose we have observed that 356C54 was less effective than 139C55 The only difference between these two compounds is that the latter has one methylene group less between the benzhydryl grouping and one of the quaternary nitrogen atoms If this methylene group is reinstated further along the chain between the two quaternary nitrogen atoms—as in a recent compound 444C55—the result is again a loss in potency

PROF MCMICHAEL I think that we should give some discussion to the question of whether oral dosage is a practical line of treatment as against parenteral dosage It so happens we have used injections but we have no emotional attachment to this if oral dosage is going to be easier and better for the patient it is very important The correspondence columns of our weekly medical journals in the latter

which is the effect of the drug. I think we agree that we have produced some peripheral vasodilatation and I think in that respect we agree with the pharmacologists

DR PERERA I do not think there has been any major disagreement in this discussion but one of my objectives is that we retain a question mark where it is indicated as a result of incomplete knowledge For example I think we are all in agreement that in certain stages of hypertensive disease drug therapy may result in prolongation of life Yet papilloedema may disappear headaches may be relieved and there may be a lengthening of survival in patients with the accelerated malignant phase of hypertension subjected to *sympathectomy* who fail to get a drop in blood pressure This is not a contradiction, but it suggests that other mechanisms than hypotension may be involved in the various treatments we employ

In untreated patients in the accelerated phase we are all in agreement that survival is rarely beyond two years Sympathectomy in our experience is beneficial to some 30 per cent of this group to the extent of a five year average survival In patients with progressive organic changes who are not in the accelerated phase the average survival is close to five years Hence we must wait and see whether the results of drug therapy will exceed both control series of patients and patients who receive surgical therapy Only after a comparison is made between all control groups and treatments of various sorts can we draw conclusions that are applicable to all stages of the disease

DR DORNHORST I wish to support Dr Perera I am sure his experience of these drugs is exactly that of many people who have used them although not making systematic studies of large numbers and it appears quite possible that his view far from being a minority view a it may have seemed may very well represent experience of the majority of clinicians

We accept that the real benefits of these drugs come in the accelerated or the malignant phase of hypertension I would suggest that the main point of organization would be to agree not to take the blood pressure until there is papilloedema

DR R W D TURNER (Edinburgh) For some eight years in Edinburgh we have been trying to study the effects of these drugs in a clinic set up for the purpose The evolution of their use has been similar to that of Professor Smirk we have had similarly encouraging

PROF MCMICHAEL I would confirm that Dr Murphy in collaboration also finds that the excretion of pentolinium indicates very irregular absorption We are still hesitant about going back to oral administration because of that difficulty

PROF SMIRK I am sure we all agree with Dr Perera that patients who present themselves for treatment with renal disease already well advanced are a most unpromising group however we have recently analysed our results in malignant hypertension, and in those who started treatment with moderately good renal function we found very little deterioration in the renal function over periods of four, five or six years I think we can commit ourselves to the view that in malignant hypertension the development of renal impairment is much retarded by treatment I would also like to commit myself firmly and definitely to the view that advanced Grade II and Grade III cases have a much better outlook as regards life expectancy

DR HOOD I should like to take issue with one statement of Dr Perera s he said that in cases with the most advanced renal insufficiency we might do harm to the kidney by using these drugs Below that critical level which I mentioned an endogenous creatinine clearance of a little above 20 litres per 24 hours we have three patients in all of whom we have repeatedly produced a very sharp rise of non protein nitrogen and serum creatinine and as soon as we have allowed the blood pressure to go up again the renal function has returned to the original level

We have been seeing studies in acute experiments but a chronic experiment is the one to tell in a disease like this Dr Perera suggested that the bulk of evidence showed that the primary effect of ganglion blockers would be to decrease the cardiac output and minute volume of the heart That is what happens in an acute experiment we have done similar experiments ourselves and have found that after a single large intravenous dose of hexamethonium we may get a severe decrease in cardiac output But that is a different situation from the patient receiving long term treatment

PROF MCMICHAEL The cardiac output normally falls when you stand on your feet so the cardiac output is always down when you get postural hypotension but after hexamethonium we found it to be no lower than it was before the drug had been given The only difference is that the correcting vasomotor reflexes are not working

St Mary s Hospital there are probably thirteen thousand hypertensives How many of these people will in fact develop malignant hypertension? Various estimates have been given up to as high as seven per cent but I think the most valid study was that of Bechgaard who in a ten year study of a thousand hypertensives found that five of them developed malignant hypertension (0 5 per cent) To our own hospital which serves a region of about 100 000 190 malignant hypertensives were admitted in twenty years So the risks of malignant hypertension work out on the average to about one per cent or less in a given hypertensive subject

Malignant hypertension moreover is a diminishing risk after the age of sixty after sixty five it is exceedingly rare Under the age of thirty it does occur but nearly all those patients are either nephritic or pyelonephritic so that focuses our attention on the age group between thirty and sixty

Heart failure is certainly an indication for taking the load off the heart and that is another major indication for these drugs You must be convinced that the patient s life is seriously threatened by his hypertension before you start pushing the blood pressure down

I am glad however that Professor Smirk is taking in a wider group because someone has got to study hypertensive patients and see whether or not earlier blood pressure reduction will diminish the incidence of the complications which may come on at any time They may live thirty years without any trouble but on the other hand they may only live as many months or as many weeks before s rious trouble complicates the picture and that is our great difficulty

DR HOOD About that most important question of how to select the patient for treatment we are all agreed that malignant and complicated cases of hypertension should be treated but I tend to take a rather broader view I do not mean that the individual physician should start to treat every patient who comes along but when a group has thoroughly familiarized itself with the technical details of treatment they may extend the treatment both ways more into the advanced field and backward to the mild and moderate cases In the gross mortality among hypertensives the group of cases of malignant hypertension do not play any considerable role at all My view is that we should take the broad outlook on the problem that Professor Smirk has done and I think we are justified in doing that once we have achieved experience enough in the cases which everyone agree we should treat

The point was raised whether we are really doing something to the

results to those Professor McMichael has described in malignant hypertension though on a smaller scale our general conclusions over some years have been closer to those of Dr Perera than to any one else whom I have heard speak in the past or who has published his results

We are faced with the dilemma that we are all agreed that these drugs have an important and useful part to play in those with severe hypertension, and by severe I mean not only those with malignant hypertension but those with evidence of hypertension reflected in the heart or in the fundi with or without papilloedema We have come more and more to deplore the widespread and promiscuous use of these drugs in numerous patients in whom the only finding is that of a raised blood pressure not reflected as hypertensive disease objectively in any organ and there are thousands of patients in the world now whose lives have been rendered unhappy or miserable or who are having dangerous side effects for no proven reason I think we should probably agree that no drug has yet lived up to the claims of the manufacturers

We are then faced with this dilemma We should use drugs in severe hypertensive disease we should not use them for those merely with a high blood pressure Clearly we should be treating those patients in whom the severe manifestations might be prevented or postponed and that I think is our difficulty How can it be done except by keeping under observation without specific treatment those in whom high blood pressure is found or with only mild objective manifestations and at the same time endeavouring to have such an ascendancy over our patients that they are not rendered anxious and miserable, but have the confidence that the object of keeping them under observation is to preserve their good health for the future? It is a very difficult problem

There is only one other question I would like to raise Professor McMichael referred to improvement in the electrocardiogram that is to say regression of unequivocal signs of left ventricular hypertrophy which of course brings up the problem of how to define the early stages of such hypertrophy Our experience has been that with few exceptions the electrocardiographic signs—the accepted signs of left ventricular hypertrophy not of ischaemia—rarely regress I should be interested to know the experience of others

PROF MCMICHAEL We have rather dodged the issue as to when hypotensive drugs are really indicated In a population unit of one hundred thousand and extrapolating from the population studies at

of these drugs is on the blood pressure rise that would occur with exercise because if you are just measuring the blood pressure in a casual or basal way you may not be getting the necessary informa tion about what happens to the patient s blood pressure when he gets up and goes about his ordinary daily activities It seems to me that ought to be taken into account

DR HOOD We have made some observations using oral hexa m thonium in a dosage which was insufficient to produce any decrease in the resting horizontal blood pressure We showed that during work on a bicycle ergometer (300 KgM) there was a 70 mm difference in the peak reached and there was a striking difference in the post-exertional drop in blood pressure in that during the ganglion blocking the drop was very much more marked than before

If two work periods are taken the result is augmented in the second period If the ganglion blocking dosage is pushed a little furthe a level can be reached where during the work period the blood pressure is lower than in the horizontal resting position while still not exceeding a clinically tolerable do age

PROF MCMICHAEL We too have made some studies on this and certainly immediately after exercise the blood p essure can fall pro foundly in the patient under methonium The patients sometimes note that if they stand still after walking up stairs or other exertion they feel faint so that I think that the pressure does not rise so high during exercise and certainly falls more profoundly afterwards

hypertensive disease Schroeder, in a recent report, picked out 79 cases where he thought he had achieved excellent blood pressure control and calculated how much hexamethonium was needed to maintain that excellent control At the end of the first year, 75 per cent of the initial dose was needed, at the end of the second year something like 55 per cent was needed at the end of the fourth year about 35 per cent of hexamethonium was needed, and approximately corresponding figures for hydralazine in a few patients he was able to omit the treatment entirely We were struck that by using a rather similar approach our requirements of pentolinium have gone down very much in the fourth fifth or sixth year and to our way of reasoning there cannot be any other explanation for this than that underlying hypertensive process has been in some way, affected by the treatment

DR CONWAY I should like to ask whether there is any association in Professor McMichael s series between the effectiveness of the hypotensive agent on the patient and the duration of survival I feel if we are going to say that reducing the blood pressure is prolonging life, the effect of the hypotensive drugs should be demonstrably greater in the surviving patients

PROF MCMICHAEL Two of the patients who have now survived beyond five years have been women who have required the biggest doses of all One of them at one stage required a single injection of about a gram of hexamethonium to bring the blood pressure down—a large dose involving a very large bulk of fluid—and that patient is doing exceedingly well now five and a half years after treatment was begun There is no correlation in the dosage needs and the length of survival One of the astonishing things is the enormous variation in the individual requirements of these drugs There is no standard dose you must work up to the dose which brings down the pressure

PROF A ST G HUGGETT (London) Has anybody had experience of drug therapy when surgical therapy has failed '

PROF SMIRK We have about twelve patients whose sympathectomies failed and they responded very well to drug therapy They react to smaller doses of ganglion blocking drugs than people who have not had a sympathectomy

PROF C A KEELE (London) I would like to know what the effect

4TH SESSION
(AFTERNOON)
FRIDAY APRIL 6TH

Chairman Professor Clifford Wilson

THE CONTROL OF VASCULAR TONE IN HYPERTENSION

CONTROL OF VASCULAR TONE IN HYPERTENSION

CLIFFORD WILSON

CLINICAL AND EXPERIMENTAL INDICATIONS

THERE is very little common ground between our knowledge of the physiological regulation of normal vascular tone and clinical and experimental observations in man and animals with high blood pressure In attempting to bridge this gap investigation has proceeded along three main lines

(1) Observation of the clinical phenomena of human hypertension with particular reference to its origins natural history and reversibility

(2) Experimental studies of the peripheral vascular system in man using in particular blood flow techniques

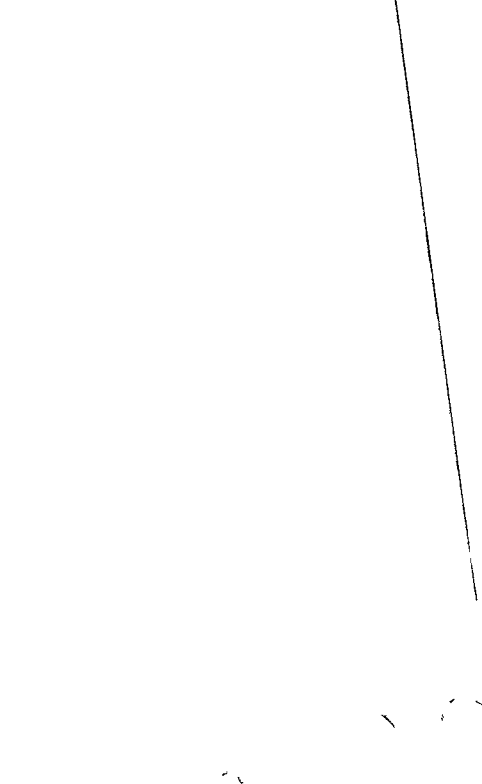
(3) The study of experimental hypertension in animals especially of renal hypertension produced by the Goldblatt technique

I shall deal chiefly with the first of these three aspects of the problem the clinical phenomena of hypertension in man

Hypertension is a disturbance of function common to a variety of disorders including renal disease endocrine diseases especially those affecting the adrenal cortex and medulla coarctation of the aorta and pregnancy toxaemia When no such primary disorder is found we speak of essential hypertension and this is the largest group of all

For the clinician however the most pressing problem is that of *chronic persistent* hypertension for it is this form of high blood pressure which leads to cardiovascular hypertrophy and accelerates arterial degeneration by which reason it has become one of the most serious causes of morbidity and mortality

It has become a habit particularly in recent years to emphasise the multiplicity of factors which appear to play an aetiological role in the production of high blood pressure The list includes psychological stress vasomotor reflexes the pressor amines renin kidney disease adrenal cortical hormones age sex and finally or perhaps one should say initially heredity so that the idea of finding a single



an increase in circulating adrenaline and noradrenaline can be demonstrated Moreover the associated symptoms—palpitations pallor of the skin nausea and abdominal pain are the direct result of excess of circulating pressor amines and the whole syndrome can be reversed by adrenergic blocking agents In recent years however attention has been directed to atypical variants of this classical picture Thus the presenting feature may be *persistent* rather than *paroxysmal* hypertension or alternatively the blood pressure may remain high between crises or occasionally the patient may present with the fully developed picture of malignant hypertension

Persistent hypertension in phaeochromocytoma may of course be attributable to a persistent high level of circulating pressor amines this is not always the explanation for in some cases high blood pressure persists when the tumour has been removed and adrenaline and noradrenaline levels have returned to normal Thus a *second mechanism*—the mechanism of established hypertension—has come into play and remains operative after the primary cause of the hypertension has been removed This stage of established hypertension *differs in no* recognisable respect from chronic essential hypertension In fact unsuspected adrenal medullary tumours have occasionally been discovered when lumbo dorsal sympathectomy has been performed for supposedly essential hypertension

This rare disease provides us therefore with unequivocal evidence of acute hypertension of known hormonal origin developing into chronic hypertension with a change in the physiological mechanism which continues to operate when the primary cause is removed

ESSENTIAL HYPERTENSION

Turning now from the vaguely known to the clearly unknown let us consider the origins chronic phase and malignant termination of essential hypertension The mode of development of essential hypertension is without doubt the most obscure problem in the whole field For nearly forty years it has been recognised that under the influence of environmental stimuli particularly anxiety the blood pressure as recorded casually may be higher than the resting or basal level This applies both to normotensive and hypertensive subjects but as the diastolic level rises the blood pressure becomes less labile Basal pressures can be obtained under conditions of mental relaxation or by administering sedatives or ganglion blocking drugs but even then some lability remains i e the basal pressure is not absolute Even when s vere hypertension is well controlled by

physiological disturbance to account for the common forms of hypertension has come to be regarded as an over simplification

Yet I believe a study of the natural history of hypertensive disease in the various conditions I have mentioned, leads us to the conclusion that however dissimilar the modes of origin hypertension in its fully developed and chronic state presents as a single disorder with no distinguishable differences in clinical picture morbid anatomy or, as far as we know in the underlying physiological disturbance of the cardiovascular system Moreover this final common pathway of the different hypertensive diseases may lead to a remarkable variant in vascular behaviour, the so-called *malignant form of hypertension*, which in terms of functional pathology has been one of the most profitable fields of experimental observation Malignant hypertension may be described as a late or terminal stage of most forms of hypertensive disease The blood pressure is unusually high the diastolic often 140 mm or more Characteristic changes appear in the optic fundi and of these papilloedema is the diagnostic clinical sign Vascular disturbances in the brain may lead to the syndrome of *encephalopathy* with blindness disorientation convulsions and coma paroxysmal dyspnoea is due to left heart failure and progressive renal damage results from acute fibrinoid necrosis of the arterioles and endarteritis of the small arteries of the kidney Similar arteriolar lesions are found in other abdominal viscera and in the brain They are a consequence of the hypertension and progressively increase in frequency and severity unless som reduction in blood pressure is brought about

I shall try to assemble the main clinical facts which seem to me to support this unitary concept of chronic hypertension taking in turn three types of disease associated with high blood pressure essential hypertension renal hypertension and phaeochromocytoma In each disease I shall deal with the three main phases of the natural history first the stage of onset second the stage of established or persistent hypertension and lastly the malignant phase I have separated these three phases because it seems likely that each has its special disorder of peripheral vascular behaviour

PHAEOCHROMOCYTOMA

Although this is probably the rarest hypertensive disease it is the most suitable starting point since it is the only one in which we are reasonably certain of the cause In the classical case a tumour of the adrenal medulla gives rise to paroxysmal hypertension and

there is a generalised increase in peripheral resistance which cannot be attributed to sympathetic hypertonus or to any known humoral agent The increase in peripheral resistance is limited to the systemic circulation the absence of associated pulmonary hypertension would appear to exclude a circulating pressor substance as the aetiological agent unless its action is selective A further remarkable but unexplained physiological adaptation is evident from the observation that the aortic and carotid sinus reflexes are still active but the threshold stimulus appears to be set at a high level

Obstructive lesions of the renal arterial system can be excluded as the cause of chronic essential hypertension at any rate in so far as these can be observed microscopically for such lesions are now known to develop as a result of the hypertension There is of course the possibility that some form of functional renal circulatory deficiency may play an aetiological role The fact that clearance studies demonstrate a reduction in renal plasma flow only in severe or advanced cases of essential hypertension does not preclude this possibility for in established experimental renal hypertension clearance studies have shown that blood flow through the clamped kidney may be within normal limits

Whatever the nature of the peripheral vascular disorder in essential hypertension there are certain recognised factors which have an aetiological significance or may influence the natural history Inheritance is an undoubted factor The *incidence* of the disease increases with age Women tolerate all forms of chronic hypertension better than men Obesity predisposes to hypertension and weight reduction is often an effective form of therapy It is doubtful however whether a more informed understanding of these genetic and environmental factors will reveal the intimate nature of the vascular disorder which determines chronicity

This brings me to the question of reversibility of essential hypertension Spontaneous reversal is reported but only in a small minority of cases A prompt and lasting reversal or a marked reduction in blood pressure may follow cardiac infarction or a cerebral vascular accident but in neither case is the mechanism understood Reversal by extensive sympathectomy is usual in benign essential hypertension but a return to pre operative levels within months or years is not infrequent Occasionally the lowering of the blood pressure produced by hypotensive drugs may persist when therapy is discontinued This is in my experience a rare phenomenon and the possibility of spontaneous reversal cannot be excluded Of particular interest in reference to our later discussion is the reversal

ganglion blocking agents environmental stress may produce a large upswing of the blood pressure These observations serve to show that emotional lability of the blood pressure cannot be definitely ascribed to any recognised physiological mechanism Recent investigations by WOLFF and his collaborators have emphasized the role of particular forms of mental stress in provoking reversible episodes of hyper tension these workers found no fundamental difference in response in normotensive and hypertensive subjects

Physiological studies of emotional and reversible hypertension are only relevant to the problem of essential hypertension if the former can be proved to be a precursor stage of the latter On this point the evidence is not conclusive The analogy with the hyper tension of phaeochromocytoma is a suggestive one and it is for this reason that I have discussed the two conditions in this sequence but so far as I am aware there is no direct evidence, clinical or biochemical that emotional swings of blood pressure are due to over production of adrenaline and noradrenaline Essential hyper tension is a common condition anxiety reactions are still more common and the two must coexist in a large section of the popula tion But many patients, especially women continue for many years with intermittent hypertension and yet fail to develop persistent elevation of the basal diastolic pressure or the cardiovascular hypertrophy which is its anatomical counterpart Nor have we any proof that such patients are more liable to arterial degeneration than normotensive subjects Moreover essential hypertension is occasion ally observed to develop rapidly and even to pass into the malignant phase in a short space of time from a previously normal blood pressure level

If the initial stage of essential hypertension is obscure the established stage is in my view well defined as a pathological state It is unprofitable to argue where the dividing line should be drawn between normal and raised blood pressure Like many other diseases particularly of metabolic or endocrine origin essential hypertension is a disturbance of the homeostatic mechanism of the body and as with other such disturbances of dynamic equilibrium there may be no precise definition of the point of departure from the normal For our present purpose it is enough to recognise that a persistent elevation of systolic and diastolic pressures under basal conditions is a clear indication of the established stage of this disease This is the commonest chronic hypertensive state but it has no specific features which distinguish it from chronic hypertension arising from renal or endocrine disease Cardiac output is normal

there is a generalised increase in peripheral resistance which cannot be attributed to sympathetic hypertonus or to any known humoral agent The increase in peripheral resistance is limited to the systemic circulation the absence of associated pulmonary hypertension would appear to exclude a circulating pressor substance as the aetiological agent unless its action is selective A further remarkable but unexplained physiological adaptation is evident from the observation that the aortic and carotid sinus reflexes are still active but the threshold stimulus appears to be set at a high level

Obstructive lesions of the renal arterial system can be excluded as the cause of chronic essential hypertension at any rate in so far as these can be observed microscopically for such lesions are now known to develop as a result of the hypertension There is of course the possibility that some form of functional renal circulatory deficiency may play an aetiological role The fact that clearance studies demonstrate a reduction in renal plasma flow only *in* severe or advanced cases of essential hypertension does not preclude this possibility for in established experimental renal hypertension clearance studies have shown that blood flow through the clamped kidney may be within normal limits

Whatever the nature of the peripheral vascular disorder in essential hypertension there are certain recognised factors which have an aetiological significance or may influence the natural history Inheritance is an undoubted factor The incidence of the disease increases with age Women tolerate all forms of chronic hypertension better than men Obesity predisposes to hypertension and weight reduction is often an effective form of therapy It is doubtful however whether a more informed understanding of these genetic and environmental factors will reveal the intimate nature of the vascular disorder which determines chronicity

This brings me to the question of reversibility of essential hyper tension Spontaneous reversal is reported but only in a small minority of cases A prompt and lasting reversal or a marked reduction in blood pressure may follow cardiac infarction or a cerebral vascular accident but in neither case is the mechanism understood Reversal by extensive sympathectomy is usual in benign essential hypertension but a return to pre operative levels within months or years is not infrequent Occasionally the lowering of the blood pressure produced by hypotensive drugs may persist when therapy is discontinued This is in my experience a rare phenomenon and the possibility of spontaneous reversal cannot be excluded Of particular interest in reference to our later discussion is the revers

of established hypertension by sodium deprivation, for example, by the strict rice diet regime This reversal is only partial and sometimes fails completely but even in the malignant phase there may be a significant fall in blood pressure with disappearance of papilloedema

The *malignant phase* of essential hypertension develops in only a small percentage of cases It was 5% in a hospital series studied by KIMMELSTIEL and myself (1936), but hospital admissions must be heavily weighted in favour of malignant hypertension While the diastolic pressure is in general higher in malignant than in benign hypertension the absolute level does not seem to be the determining factor It may be that a sudden rise at a high pressure level is more significant Thus malignant hypertension is observed in about 50% of patients with chronic renal disease and in these there is often a rapid rise in blood pressure before papilloedema develops It may be relevant that the malignant change occurs relatively frequently in hypertension due to phaeochromocytoma where rapid exacerbations are common I believe that in malignant hypertension there are regional changes in vascular tone especially in the brain, retina and kidney, which differ qualitatively from the generalised increase in peripheral resistance of benign hypertension This regional vasoconstriction, or the paralytic vasodilatation which follows, may well lead to fibrinoid necrosis of the arterioles BYROM'S observations (1954) of cerebral vascular spasm during attacks of hypertensive encephalopathy in the rat support this view One of the most puzzling problems of altered physiology is the explanation of the increased intracranial pressure and papilloedema in malignant hypertension These phenomena are not simply a reflection of the high diastolic pressure level Any form of treatment which reduces the blood pressure may cause reversal of papilloedema but subsequently hypertension may return to its previous level without the recurrence of papilloedema

In my view these various observations clinical and experimental on the malignant form of hypertension support the concept of a qualitative change in the physiological state of the blood vessels from that of benign hypertension I think this is best described as uncontrolled regional vasoconstriction

In our original experiments BYROM and I (1941) produced experimental evidence that severe hypertension could produce renal vascular lesions which themselves might aggravate and perpetuate the hypertension It is likely that a vicious circle of this nature operates in advanced cases of malignant hypertension but it is

obvious that organic renal vascular changes cannot be responsible for the *initial development* of the malignant phase since all the evidence indicates that such vascular changes are secondary to the hypertension

RENAL HYPERTENSION

The early stage of renal hypertension in man is rarely observed except in acute nephritis In many respects acute hypertension in this disease differs from the acute forms already discussed It is usually of moderate severity and relatively stable Yet the pressure reverts to normal rapidly as the nephritis improves or on the other hand a sudden exacerbation of the disease may produce a sharp rise in blood pressure and lead to hypertensive encephalopathy and acute left ventricular failure These complications are usually transient and completely reversible and the diagnostic features of malignant hypertension (i e papilloedema and arteriolar necroses) are rarely seen—probably because the hypertension is short lived

The nature of the increased peripheral vascular resistance in acute nephritis is controversial and there is no consistent evidence for either a neurogenic or humoral basis By analogy it seems likely that the mode of production resembles that of acute experimental renal hypertension in animals and there is some reason to believe that this differs from the mechanism of established experimental renal hypertension

The transition from acute to chronic renal hypertension may be continuous or interrupted With a severe rapidly progressive nephritis hypertension persists after the acute attack and may increase rapidly in severity with a malignant termination within a matter of months In the more slowly progressive cases hypertension is very variable The blood pressure may return to normal after the acute stage is passed but subsequently a slight or moderate degree of hypertension is observed and this is often labile or intermittent Over the course of years persistent elevation of the diastolic level develops and the hypertensive state is then in all respects similar to that of benign essential hypertension Eventually a more or less sharp transition takes place the blood pressure rising steeply often over the course of a few months Coincidently renal function deteriorates and this is greatly accelerated when malignant hypertension supervenes

Thus in renal disease we have the opportunity to study in the same patient—over the course of months or years the transition from acute hypertension to intermittent labile hypertension to fixed

hypertension and then to malignant hypertension, and it seems likely that different physiological mechanisms underly these various disorders of the peripheral vascular resistance

Of outstanding importance is the clinical observation that chronic hypertension may develop as a result of *unilateral renal disease* This again closely resembles essential hypertension and the distinction may be made only when radiological examination reveals an abnormal kidney Removal of the diseased kidney may result in return of the blood pressure to normal even after malignant hyper tension has developed Of particular interest however are those cases in which hypertension persists after nephrectomy—about half of those so treated Here is an apparent analogy with phaeochromo cytoma—*persistence of hypertension after removal of* the primary cause A similar sequence was described by BYROM and myself (1941) in rats in which hypertension was induced by constriction of one renal artery We attributed persistence of hypertension after removal of the clamped kidney to secondary hypertensive arterial lesions in the opposite kidney Dr FLOYER will present evidence that, whatever the mechanism of this persistent hypertension, it certainly depends on the presence of an abnormal kidney I see no reason to doubt that a similar explanation holds good in most cases of per sistent hypertension after nephrectomy in man Histological evidence of hypertensive renal lesions in the opposite kidney is frequently obtained post mortem in such cases

The explanation of persistent hypertension after removal of the primary cause is obviously the crux of the whole problem of chronic hypertension Dr FOLKOW s experiments have a direct and important bearing on this question and so have the experimental observations made by Dr LEDINGHAM and Dr FLOYER I think we can exclude the possibility that generalised organic arterial changes—either hyper trophy or degeneration—contribute to this persistent hypertension for given the appropriate conditions it can be promptly reversed in both animals and in man The discovery by GROLLMAN (1943) in rats and by PICKERING (1945) in rabbits that hypertension induced by renal ischaemia might persist after *total* nephrectomy appeared to exclude a renal factor and led them to postulate an extra renal mechanism Further studies of renoprival hypertension have led to the hypothesis of a combined renal adrenal mechanism controlling peripheral vascular tone possibly by variation in the distribution of electrolytes in relation to the smooth muscle cells of the arteriolar wall Dr FLOYER and Dr LEDINGHAM will present some of the evidence they have obtained on the renal and extra renal factors

involved in the maintenance of experimental renal hypertension in the rat The outcome of these investigations led us some two years ago to turn to the study of the responsiveness of the peripheral circulation to the physiological stimulus of filling pressure under varying conditions As a result of his observations on cerebral vascular spasm in hypertensive encephalopathy BYROM also was led to the view that the responsiveness of the arterioles to physiological stimuli might well be relevant to the genesis of chronic hypertension. By an entirely different route Dr FOLKOW and his colleagues have made a similar approach from the physiological side and have obtained valuable and suggestive data supporting this hypothesis

Thus the emphasis has shifted from the role of circulating pressor substances and neurogenic factors in hypertension to a consideration of the responsiveness of the smooth muscle cells of the arterioles conditioned by changes in their immediate chemical environment It is along these lines that I believe the problem of chronic hyper tension and perhaps of regulation of the normal blood pressure may find a possible solution

To summarise this rather diffuse survey of clinical and experi mental phenomena I think the main relevant points are as follows

(1) There are diverse causes of acute hypertension of which the most important may be termed hormonal neurogenic and renal

(2) *All* kinds of acute hypertension may lead to a common form of persistent hypertension in which the physiological mechanism is different from that which operates in the acute stage This new mechanism may remain in action when the primary cause of the hypertension is removed

(3) A feature of all forms of persistent hypertension is the change from so-called benign to malignant hypertension In this variant the evidence points to a breakdown in the physiological relationship between intra arterial pressure and arteriolar resistance Excessive regional vasoconstriction particularly in the brain retina and kidneys leads to severe disturbances of blood flow and probably forms the basis of fibrinoid necrosis of the arterioles

(4) interference with the renal circulation mo t simply produced by renal artery constriction is the one type of physiological dis turbance by which the chronic hypertensive state may be reproduced in animals It seems rea onable *to assume that* this is the common factor in the various renal diseases which give rise to high blood pressure in man

(5) There is unequivocal experimental evidence that hypertension can itself produce a disorder of the renal circulation which leads to the chronic hypertensive state

(6) Whatever the nature of the renal pressor mechanism there is strong evidence which suggests that an extra renal factor is involved and that renal hypertension results from a breakdown of the regulatory function which the kidney normally exercises on the extra renal factor

REFERENCES

BYROM F B (1954) *Lancet* ii 201
GROLLMAN A HARRISON T R and WILLIAMS J R (1943) *Amer J Physiol* 139 293
KIMMELSTIEL P and WILSON C (1936) *Amer J Path* 12 45
PICKERING G W (1945) *Clin Sci* 5 229
WILSON C and BYROM F B (1941) *Quart J Med* 10, 65

STRUCTURAL, MYOGENIC, HUMORAL AND NERVOUS FACTORS CONTROLLING PERIPHERAL RESISTANCE

BJORN FOLKOW

In any region maximal blood flow at a given perfusion pressure and blood viscosity is in the final instance determined by the morphology of its vascular bed i e by the resistance to flow offered by the vessels when their smooth muscle cells are *completely* relaxed It is reasonable to assume that this maximal blood flow capacity is to some extent related to the maximal nutritional needs of the tissue concerned Setting out from this structurally determined baseline the extent of vascular smooth muscle tone as controlled by the interaction of nervous blood borne and local influences will determine the actual resistance to blood flow

THE REGULATION OF VASCULAR TONE IN THE NORMAL INDIVIDUAL

It is of interest to know to what extent different types of excitatory and inhibitory influences contribute to the establishment of vascular tone in various regions in a normal organism It is often taken more or less for granted that vascular tone is primarily a matter of vasomotor fibre activity and that any remaining tone after acute cutting of the vasoconstrictor fibres is a consequence of constrictor agents in the blood stream There are however very few studies available that have in detail investigated this problem Observations made on e g restricted cutaneous vascular areas are usually assumed to be valid for the vascular tree in general (see e g LE COMPTE 1941) which by no means necessarily is the case To study this question more closely experiments have been performed on cats with an analysis of the regulation of the tone of the vessels in the skeletal muscles as compared with the skin of the paw where the vascular bed is dominated by numerous arteriovenous anastomoses

The constrictor fibre activity and consequently its *contribution* to vascular tone is naturally enough a highly variable factor depending on the actual balance of central and reflex influences on

the medullary vasomotor centre In animals under light anaesthesia, carefully prepared and kept in good condition as far as is possible experimental evidence indicates that resting sympathetic tone is maintained by an impulse flow of one to three impulses per second (*for lit see* FOLKOW *1955*) Cutting the vasomotor nerves to the mentioned regions results in an increased blood flow to the skeletal muscles by 50–100 per cent and to the paw by some 100–800 per cent, the variation of the latter figure depending on the actual heat exchange balance of the animal The bigger figures for increase of blood flow in the paw are a consequence of the fact that a given vasoconstrictor fibre discharge has a much more powerful effect in *this region than in the muscles* (CELANDER and FOLKOW *1953*)

To what extent does vascular tone remain after acute sympathetic block in the resting organism? This remaining tone will here throughout be called *basal vascular tone* Obviously enough such a question can only be answered by a correlation of the peripheral vascular resistance for any given region at the basal tone level with the resistance that remains after complete relaxation of the vessels *Acetylcholine, ATP or nitrites are known to be able to induce* powerful vasodilatation in both areas studied If supramaximal concentrations are used in close arterial injections a complete vascular relaxation should be obtained and from this blood flow level the peripheral resistance at maximal dilatation can be calculated Such an analysis indicates that the basal tone of the vessels of the skeletal muscles is considerable as the peripheral resistance can here *be further decreased some 500–700 per cent The vessels of the paw*, on the other hand seem to be almost maximally dilated after acute sympathectomy as in this region the peripheral resistance can only be further decreased approximately 20–50 per cent (CELANDER and FOLKOW, *1953* LOFVING and MELLANDER *1956*) *This latter* circumstance is not a consequence of low sensitivity to dilator agents as a prompt and powerful dilatation of the paw vessels is easily obtained by dilator drugs if only an initial vascular tone is created by, e g, low frequency stimulation of the constrictor fibres This is probably also true for man as here acute sympathetic block increases blood flow in the muscles only about one hundred per cent (BARCROFT and SWAN 1953) *while e g muscular work is known to be able to* increase the flow ten to fifteen times On the other hand acute sympathetic block of the finger vessels in man which correspond to the pad vessels in the cat s paw results in what seems to be a nearly maximal dilatation (for lit see BARCROFT and SWAN 1953 FOLKOW, 1955)

To take some other vascular beds it is known from studies of the coronary (GREGG 1950) and the cerebral circulation (SCHMIDT 1950) that regional vasomotor fibre block does not to a significant extent increase the blood flow Nevertheless increased metabolism of the respective tissues or injection of dilator agents are able to dilate these vascular beds quite considerably Therefore as in the skeletal muscles the basal tone seems to be pronounced in these regions comparatively little influenced by constrictor fibre activity

If basal vascular tone were primarily due to constrictor agents in the blood stream it should be expected that the cutaneous arterio venous anastomoses should be very insensitive to such agents because—as mentioned—their basal tone is by far the lowest However the vessels of the paw show a greater sensitivity to biogenic constrictor agents such as adrenaline noradrenaline angiotonin serotonin and vasopressin than do those of e g the skeletal muscles (LOFVING and MELLANDER 1956) Under such circumstances it is very difficult to believe that basal vascular tone is a consequence of blood borne constrictor agents Neither is it likely that significant amounts of such factors are present in normal blood under con ditions of rest

Basal vascular tone must then be a consequence of a local mechanism There is in fact very good evidence of automaticity of smooth muscle cells in general (see BOZLER 1948) and those in the vascular walls do not seem to form an exception (FOLKOW 1955) It is obvious that an inherent activity of va cular smooth muscle cells must create a certain vascular tone The distending force of the blood pressure seems to exert a certain excitatory influence on the activity of the smooth muscles too (BAYLISS 1902 FOLKOW 1949 HILTON 1953 WOOD *et al* 1955) Automaticity seems to be negligible only in certain highly specialized smooth muscle cells e g the intrinsic muscles of the eye Here an intimate central nervous control has been established and local factors cannot be allowed to interfere with this central regulation The smooth muscle cells of the cutaneous arteriovenous anastomoses are specialized in a similar way to serve the central control of the heat loss and are also quite dominated by their constrictor fibres An absence of auto maticity would also here be natural as it would otherwise have interfered too much with the centrally induced adjustments If this is so it is easily explained why the paw vessels are almost maximally dilated after sympathetic block

To sum up basal vascular tone seems to be primarily due to a smooth muscle automaticity, while the influence of blood borne

constrictor agents seems to be negligible under resting conditions The importance of such agents for the establishment of vascular tone has often been overestimated, and even the secretion from the suprarenal medulla is here of small relevance under basal conditions (see FOLKOW, 1955) *On strong reflex activation of the sympathetic* nervous system the direct effect of the constrictor fibres dominates the vessels to such an extent that under such circumstances too, an increased secretion from the suprarenal medulla becomes of almost negligible importance (CELANDER, 1954) The main field of *action of these hormones is probably to be found in their control* of specific events of the carbohydrate metabolism

Superimposed on the basal tone the constrictor fibres exert a wide range of control, though in extent highly variable in different regions There is a general trend towards an inverse relationship *between constrictor fibre dominance and basal vascular tone* Vessels serving the local nutritional needs of tissues highly important for the maintenance of life are little influenced by the constrictor fibres A "blood flow reserve" is here created mainly by a marked basal tone The control of such a vascular area is therefore largely *withdrawn from vasoconstrictor reflexes and the strictly locally* controlled blood flow reserve' is easily mobilized to the extent needed during increased activity of the tissue At the other extreme there are the cutaneous arteriovenous anastomoses of negligible importance for local tissue nutrition but specialized to serve the *centrally directed body temperature regulation These vessels are* completely dominated by their constrictor fibres with no or very little basal tone

SOME ASPECTS OF THE REGULATION OF THE PERIPHERAL RESISTANCE IN THE HYPERTENSIVE INDIVIDUAL

What happens to the control of vascular tone in hypertensive disease? It is obvious that several factors might increase smooth muscle activity such as an increased vasoconstrictor fibre activity increased amounts of constrictor agents in the blood and (or) increased reactivity of the vascular smooth muscle cells to constrictor influences These alternatives for explaining the increased vascular resistance all imply increased smooth muscle tone and have attracted by far the greatest interest in recent years Generally it is taken for granted that the baseline is unchanged i e that the vascular resistance at *complete* smooth muscle relaxation is the same

as in normal individuals If however this is no longer the case there is no common reference point for an evaluation of the extent of increased smooth muscle tone

Suppose that a secondary hypertrophy of the wall elements has caused a generalized wall thickening that partly takes place at the expense of the lumen Such a change is not *a priori* quite unlikely as it might be looked upon as an example of an adaptive structural process the other extreme of which would be an outgrowth with a

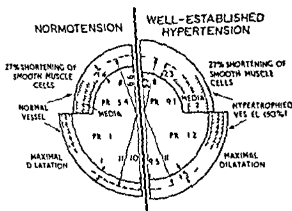


Fig 1 A schematic drawing illustrating the consequences for the resistance to blood flow in a given vessel after wall hypertrophy to a slight extent has interfered with the lumen at maximal dilatation Note also that a given shortening of the smooth muscle cells will *increase the resistance* to blood flow considerably more in the hypertrophied vessel The relative dimensions chosen are of course arbitrary though they may not differ too *much from* those of a systemic small artery

widening of the vascular tree as a response to lasting lowering of blood pressure Few quantitative data are available but it seems in fact as if such a process takes place distally to an arterial obstruction Concerning the proposed hypertrophic change, let us take some arbitrary figures and assume that the hypertrophy has interfered with the lumen to such an extent that the internal diameter of the *maximally* dilated vessel is decreased as little as five per cent The haemodynamic consequences of such a small narrowing will nevertheless be pronounced as the resistance to flow of such a completely dilated vessel will be raised about twenty *per cent* (Fig 1) Further-what is also important to realize—the resistance would remain raised as compared with a normal vessel for any level of smooth muscle activity

This possible effect of hypertrophy is however not its only consequence for the functional equilibrium of the changed vessel It can also be calculated that—for any given shortening of the smooth muscle cells—the resistance of the hypertrophied vessel would in fact be increased proportionally *more* than in a normal vessel This is because a bigger tissue volume must now be situated inside the main line of force for the smooth muscle layer This bigger tissue volume must at smooth muscle contraction be pushed towards the lumen and therefore cause a more pronounced narrowing In other words at one and the same degree of smooth muscle activity the hypertrophied vessel must for purely mechanical reasons, exhibit an intensified vasoconstrictor effect as compared with a normal thin walled vessel

This latter consequence of vascular wall hypertrophy is not dependent on the possibility that there might also be a hypertrophic interference with the lumen already at complete maximal dilatation Possibly the often discussed hypersensitivity or increased ' re activity of the vessels in hypertension is at least partly a consequence of such a structural change It should be remembered that we do not measure the actual shortening of the smooth muscle cells but their net effect on the vascular lumina, and a changed wall to lumen ratio may change the whole picture On the other hand this does not imply any vascular 'rigidity' or sclerosis', and the decrease of distensibility that must be associated with a hypertrophic increase of wall tissue mass should be balanced by the increased distending pressure as long as degenerative lesions have not changed the very elements that build up the vascular wall It merely means a new equilibrium at a higher level but with a normal range of vascular reactions

Hypertrophic vascular changes as a response to increased blood pressure have been described by numerous investigators (e g KERNOHAN *et al* 1929 FERGUSON and VARCO 1954) Later on they are followed by the well known vascular lesions especially in regions like the kidneys For the present purpose only the haemodynamic consequences of a generalized vascular hypertrophy will be examined It should then be pointed out that such a structural change very well might exert significant haemodynamic effects long before it can be convincingly demonstrated by histological techniques In morpho logical studies of vascular hypertrophy the hazard of not knowing either the exact *in vivo* lumen or the extent of smooth muscle contraction at the moment of tissue fixation makes it almost impossible to tell whether there really is a definite change except in

more advanced cases It seems to be in line with the discussed haemodynamic effects of hypertrophy of the vessels that when a fraction of the pulmonary vascular tree is exposed to increased blood pressure the vessels show a hypertrophic change and also evidence of an increased resistance to blood flow (FERGUSON and VARCO 1954) The increased resistance can hardly in the type of exp riments used by these authors be ascribed to either nervous factors or increased amounts of vasoconstrictor agents in the blood

Setting out from these theoretical considerations an attempt was made to put the suggested mechanism to an experimental test (FOLKOW GRIMBY and THULESIUS 1956) The general idea was simply to compare the peripheral resistance of a vascular region at complete maximal dilatation in normal and hypertensive subjects One of the main difficulties was how to be sure that the vessels really were maximally dilated Forearm blood flow was measured by a plethysmographic method with the hand circulation excluded and the perfusion pressure was recorded in the other arm at the moment of blood flow measurement Intense vasodilatation was induced by the combined action on the forearm vessels of increasing periods of ischaemia (two five ten and sometimes fifteen minutes) with increasing amounts of work of the forearm muscles during the last minute of ischaemia (twenty to fifty strong hand contractions) Further to facilitate the dilatation of the cutaneous vessels the temperature of the water in the plethysmograph was kept at 42–43 C Under the e circumstances the blood flow increase had already after five minutes of ischaemia reached some ninety per cent of its highest obtainable value both in normal and hypertensive subjects It might be argued that the concentration of dilator agents may not have been significantly increased by prolonging the period of ischaemia from five minutes to ten minutes However all subjective phenomena pointed to a stronger ischaemia at ten minutes of vascular occlusion and furthermore the dilator response was then much more prolonged than after a period of only five minutes of ischaemia An attempt was also made in most cases to facilitate the dilator responses by putting the periods of ischaemia so close together that the blood debt was not repaid in between but in spite of this the blood flow could not be further increased It therefore seemed justified to believe that maximal vasodilatation really was reached both in normal and hypertensive subjects

When acute hypertension was induced in normal subjects by steady infusion of noradrenaline the blood flow increase following the above mentioned procedures for eliciting maximal dilatation

was raised proportionally to the increased mean blood pressure In other words, the peripheral resistance in the forearm vascular bed remained essentially the same at maximal obtainable dilatation, in spite of the fact that now there were increased amounts of vaso constrictor agents in the blood (see Fig 2 and 3) This is to be expected if the accumulation of dilator agents was pronounced enough easily to overcome the increased smooth muscle tone In

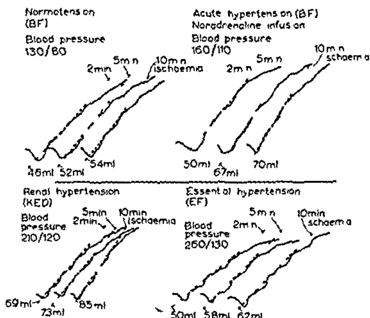


Fig 2 Plethysmographic recordings of forearm blood flow when attempts are made to induce definite maximal dilatation of the vessels by exposing them to the procedures described in the text Upper left a normotensive individual upper right the same individual made acutely hypertensive by intravenous infusion of noradrenaline Below two cases with chronic hypertensive disease

some earlier studies (PICKERING 1936 WILSON and PRINTZMETAL, 1936 WILKINS and EICHNA 1941) a similar line of approach has been used but to judge from the present figures for maximal blood flow the procedures utilized to induce vasodilatation in these studies were only exceptionally sufficient to induce a definitely maximal dilatation

One of our main technical difficulties was in fact caused by the huge blood flows as they led to an almost immediate and marked venous pressure rise if no special precautions were taken Such a venous pressure rise will of course rapidly decrease the effective

perfusion pressure and make it impossible to get anything like straight line curves and thus reliable blood flow recordings There fore it proved necessary to increase the capacity of the forearm veins to tak^ up the huge blood flows with as little venous pressure rise as possible This was done either by raising the arm well above

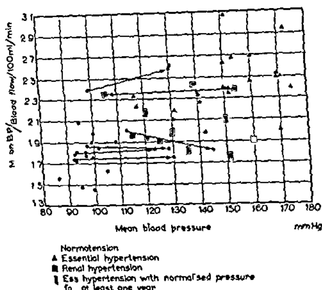


Fig 3 A diagram illustrating the correlation between the vascular resistance per 100 ml of forearm tissue at maximal obtainable vasodilatation and the mean blood pressure of the individuals measured in the other arm at the moment of recording the blood flow The arrows that connect two points in the diagram illustrate the shift in mean pressure and resistance in acutely induced hypertension in normotensive individuals In one of the renal hypertensive cases the arrow indicates the shift in mean pressure and resistance after about three weeks of treatment with hypotensive drugs For further explanation see text

heart level just before arterial obstruction or—still better—by exposing the forearm to a positive pressure of 75–100 mm of mercury which emptied the veins very effectively if the hand circulation was first obstructed completely so that no extra blood was trapped in the hand veins Thereby it proved possible to collect a somewhat bigger inflow of blood in the forearm veins than that corresponding to a two per cent increase of forearm volume a figure which forms the upper limit for reliable blood flow recordings under circum stances where the veins have not been emptied by some special

device (GREENFIELD and PATTERSON, 1954) In spite of blood flows that not seldom amounted to 60–70 ml per minute per 100 ml of tissue, the venous pressure in the forearm did not then increase significantly until after 3–4 seconds (CELANDER 1956) This means a 3–4 per cent increase of arm volume with little venous pressure rise at best After this short interval the venous pressure started to rise very rapidly which means that under all circumstances the curves will flatten out after 3–4 pulse beats when such big flows are recorded Obviously this must make calculations of the actual flow difficult even if one always follows exactly the same procedures Such difficulties seem to be unavoidable but it follows that great care must be taken in interpretation of the results We therefore prefer to look upon this study rather as suggestive evidence of a certain structural interference with blood flow in well established hypertensive disease and by no means as a definite experimental proof

Fig 2 illustrates a series of blood flow curves taken from technically satisfactory recordings in a normotensive individual made acutely hypertensive and in two cases of hypertensive disease, one of renal origin and one essential

In Fig 3 the relation between the vascular resistance of forearm vessels at maximal obtainable dilatation and the mean blood pressure of the subjects is given It is seen from this figure that even under circumstances where smooth muscle activity should be completely eliminated the resistance remains moderately raised at least in well established essential hypertension while—as mentioned —this is not the case in acute hypertension caused by noradrenaline infusion Cases classified as definite renal hypertensives (e g due to *cystic kidney degeneration or other types of kidney malformations* chronic pyelonephritis etc but generally with no positive family anamnesis for hypertension) are closer to the normal material It is of course pure hazard to speculate on the background of this difference but it is tempting to assume that most cases with essential hypertension might have a somewhat more pronounced generalized hypertrophy of the vascular walls Physically these subjects often show a mesomorphic constitution which might imply also a more pronounced tendency to react with hypertrophy of tissues exposed to increased load which then in its turn might have some bearing on the inheritable element of this variant of *hypertensive* disease

Little is known about the possibilities of regression of a hypertrophic vascular change but they might be good if only the increased

pressure is eliminated provided that degenerative lesions are not too advanced In a small group of hypertensive cases many of which had previously had severe hypertension but where therapy with hypotensive drugs had been so successful that for at least a year they had been kept at an almost normal blood pressure, the peripheral resistance at maximal dilatation was almost the same as in normo tensive cases (Fig 3) From the figure their actual blood pressure might appear high enough but this is a consequence of the rather strenuous experimental procedures Their resting pressure level is more near normal blood pressure values The rather low peripheral resistance at maximal obtainable dilatation might be due to a true regression of a hypertrophic vascular change Clinical observations of these cases also support the view that there must here have been a regression of vascular changes as in some of the cases too rapid falls of the pressure at the beginning of therapy had dangerous con equences e g for cerebral or myocardiac blood supply while later on they could tolerate much stronger reductions in blood pressure (see HOOD *et al* 1955)

It is difficult to deduce from the data in Fig 3 the exact proportion of the increased peripheral resistance in chronic hypertension that might be a consequence of a morphological vascular change This is because in practically all cases studied the influence of smooth muscle activity on the resistance to blood flow was in fact artificially damped down by more or less successful therapy with hypotensive drugs Further it is necessary to know the exact wall to lumen ratio of the vessels concerned if one wants to know also to what extent a wall thickening might intensify the vasoconstrictor effect of a given smooth muscle contraction Unfortunately such an estimation must be next to impos ible It should in this connection also be pointed out that if the vascular walls also get thickened by an increased amount of tissue fluid content (see e g TOBIAN and BINION 1954) the consequences for the vascular reactions should be about the same though establishment and regression of such a change might occur more promptly than in the case of hypertrophy

The questions here taken up are mainly intended to direct some of the interest which in recent years has been largely confined to the search for constrictor agents in blood and tissue fluids towards the possible functional consequences of even a moderate but generalized hypertrophy of the vascular walls In well established hypertensive disease the increased resistance to blood flow is not necessarily a consequence only of increased smooth muscle activity It may also be significantly influ nced by a secondary vascular

hypertrophy, which—for purely mechanical reasons—as far as can be judged must contribute to the increased resistance, without at the same time implying any element of definite vascular sclerosis

REFERENCES

BARCROFT H and SWAN H J C (1953) *Sympathetic Control of Human Blood Vessels* F Arnold and Co London
BAYLISS W M (1902) *J Physiol* 28 220
BOZLER E (1948) *Experientia* 4 213
CELANDER O (1954) *Acta Physiol Scand* 32 Suppl 116
CELANDER O (1956) to be published
CELANDER O and FOLKOW B (1953) *Acta Physiol Scand* 29, 241
FERGUSON D J and VARCO R L (1955) *Circulation Research* 3 152
FOLKOW B (1949) *Acta Physiol Scand* 17, 289
FOLKOW B (1955) *Physiol Rev* 35, 629
FOLKOW B GRIMBY G and THULESIUS O (1956) to be published
GREENFIELD A D M and PATTERSON G C (1954) *J Physiol* 125 525
GREGG D E (1950) *Coronary Circulation in Health and Disease* Lea Philadelphia U S A
HILTON S M (1953) *J Physiol* 120 230
HOOD B BJÖRK S and FALKHEDEN S (1955) *Sv Lakartidn* 52 2617
KERNOHAN J W ANDERSON E W and KEITH N M (1929) *Arch Int Med* 44 395
LE COMPTE P M (1941) *Amer J Physiol* 135 43
LÖFVING B and MELLANDER S (1956) to be published
PICKERING G W (1936) *Clin Sci* 2 209
PRINTZMETAL M and WILSON C (1936) *J Clin Invest* 15 63
SCHMIDT C F (1950) *The Cerebral Circulation in Health and Disease* Thomas Springfield Ill U S A
TOBIAN L Jr and BINION J (1954) *J Clin Invest* 33 1407
WILKINS R W and EICHNA L W (1941) *Bull Johns Hopk Hosp* 68 477
WOOD J E LITTER J and WILKINS R W (1955) Circulation Research 3 581

RENAL FACTORS IN HYPERTENSION, THL RELATIONSHIP BETWEEN THE KIDNEY AND THE BLOOD PRESSURE

M A FLOYER

WHEN GOLDBLATT (1934) produced sustained hypertension by partial renal artery constriction it was thought that the problem of hyper tension would soon be solved Today however we have not yet discovered the mechanism of Goldblatt hypertension still less do we understand the relevance of this experiment to human hypertensive disease I would like to start from first principles describe some simple animal experiments discuss their meaning, and mention some similarities between these experimental results and observations on patients with hypertension

Let us begin with the simple Goldblatt experiment in which one renal artery is partially constricted and the opposite kidney removed This animal develops persistent hypertension For a long time it was thought that these observations could be explained by the renin angiotonin mechanism In the early phase of hypertension following renal artery constriction renin can be demonstrated in the circulation (HAYNES and DEXTER 1947) and at this stage removal of the kidney results in the return of blood pressure to normal in a short time (PICKERING 1945) I shall not discuss the evidence about the nature of the mechanism of the early stage of experimental renal hypertension but will state my view that the early phase may sometimes but not always be caused partly by a pressor substance liberated from the kidney (FLOYER 1955) But whatever this mechanism may be renal hypertension in the later stages is certainly not maintained by a renal pressor substance Renin is said to disappear from the circulation with time although the hypertension persists or increases (HAYNES and DEXTER 1947) The most important observation however is that in the later stages nephrectomy does not restore blood pressure to normal PICKERING (1945) showed that in rabbits with renal hypertension of one week s duration total nephrectomy restored the blood pressure to normal in a few hours but in animals with eight weeks hypertension this operation did not affect the blood pressure

which remained raised until shortly before the rabbit died We have shown that total nephrectomy in rats with hypertension of 2–6 days duration restores the blood pressure to normal within 12 hours a subsequent rise occurs (FLOYER 1955) which I will discuss later In contrast in animals with hypertension of more than 2 weeks duration the blood pressure after nephrectomy shows only a transient fall compatible with the shock of the operation after this the blood

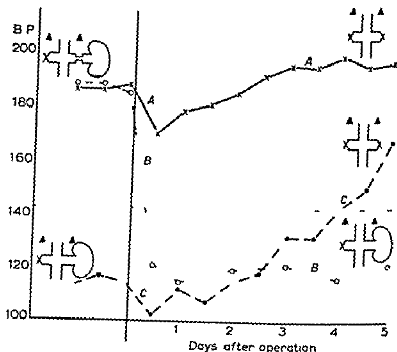


Fig 1 Curve A Effect of total nephrectomy in rats with chronic hypertension
Curve B Effect of removal of clip in rats with chronic hypertension
Curve C Effect of total nephrectomy in normal rats
(Reproduced by kind permission of the Editor of Clinical Science)

pressure persists at or above the previous level until a few hours before the animal dies (Fig 1 Curve A) Thus after a short time experimental renal hypertension becomes irreversible by neph rectomy

The possible explanations of these observations can be grouped under three headings

I The initial hypertension is due to a renal pressor substance and that later a change occurs in the set of the sympathetic nervous system maintaining the blood pressure at a high level independently of the kidney

2 Irreversible narrowing of the peripheral arterioles develops after a few weeks hypertension

3 A change occurs in the arterioles either in tone reactivity or in the actual size of the muscle cells which is reversible but which is maintained by some mechanism other than a renal pressor substance or the sympathetic nervous system

The observation which excludes the first two possibilities is that removal of the renal artery constriction always restores the blood pressure to normal even very chronic hypertension can be reversed by restoring normal circulation to the kidney BYROM and DODSON (1949) showed that in rats with a single clipped kidney and with hypertension of 12 weeks duration the blood pressure could be restored to normal in 12 hours if the constricting clip was removed BLACKETT and SELLERS (1951) reported a rather slower but nevertheless complete fall to normal following removal of the clip in rabbits with chronic renal hypertension We have found that provided the kidney is not infarcted or otherwise damaged removal of the constricting clip restores the blood pressure to normal within 48 hours (usually in a much shorter time) in rats with renal hypertension of up to a year s duration Fig 1 contrasts the fall to normal of the blood pressure after removal of the clip (Curve B) with the persistent hypertension after nephrectomy (Curve A) in rats with chronic renal hypertension

This indicates that renal hypertension remains reversible by removal of the constriction from the renal artery and excludes the possibility that changes in the blood vessels or in the sympathetic set can maintain the hypertension independently of the kidney I will return to a discussion of the mechanism of renal hypertension later

In a further study of the reversibility of renal hypertension (FLOYER 1951) we have repeated and extended an experiment first performed by WILSON and BYROM (1939) who showed that hypertension could be produced in the rat by partial constriction of one renal artery without removal of the opposite kidney They found that after a few weeks hypertensive vascular lesions developed in many organs but that these did not occur in the kidney with the renal artery constriction (the clipped kidney) They presumed that the constricting clip protected the clipped kidney from the high blood pressure If the clipped kidney was excised at an early stage before the untouched kidney was affected the blood pressure was restored to normal but if much damage due to these vascular lesions occurred in the untouched kidney hypertension persisted after

removal of the ' clipped kidney Wilson and Byrom concluded that vascular lesions rendered parts of the kidney ischaemic and that in this way the untouched" kidney could maintain hypertension

We used rats with hypertension of between 20 and 50 weeks duration produced by constriction of one renal artery without *removal of the opposite kidney All animals were subsequently shown*

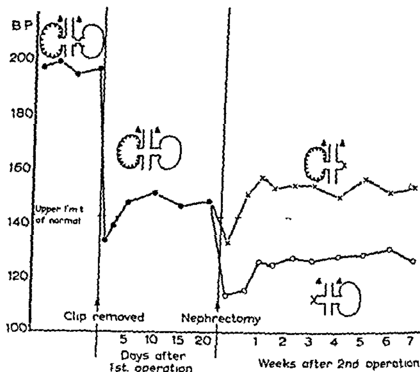


Fig 2 Effect of removal of clip and of subsequent removal of either kidney in rats with hypertension of 20–50 weeks duration
(Reproduced by kind permission of the Editor of the Ciba Foundation Symposium on Hypertension 1954)

to have considerable vascular damage in the untouched kidney but the clipped kidney remained structurally normal The first procedure was to remove the constricting clip this resulted in a fall of blood pressure to a level a little above normal (Fig 2) After a period of observation the rats were divided into two groups In the first group the kidney which previously had been clipped was excised, leaving only the damaged kidney *in these animals the blood pressure* rose a little In the remaining rats the damaged kidney was was excised leaving a structurally normal kidney with normal circulation in this group the blood pressure was restored to normal This

demonstrates that in rats excision of a damaged kidney and restoration of normal circulation to a normal kidney can reverse hypertension of up to a year s duration This experiment further emphasises that any change which occurs in the peripheral vessels in chronic renal hypertension is not irreversible and that in renal hypertension the blood pressure remains under the control of the kidney

I would like to compare this last experiment with a remarkable study recently made in Boston by MERRILL and his associates (1956) Of two brothers aged 23 who were shown to be homozygous twins one had nephritis with malignant hypertension and renal failure while the other was healthy One kidney from the healthy twin was transplanted into the pelvis of the sick brother the artery and vein being joined to the internal iliac vessels and the ureter implanted into the bladder The transplanted kidney secreted urine at once and the blood urea was restored to normal in a few days Immediately after the operation the blood pressure which had previously remained at a high level for a considerable time fell to normal but a few days later it rose to levels somewhat above normal but very much lower than previously After a few months the two diseased kidneys were removed leaving only the implanted kidney this operation restored the blood pressure to normal at once and it has remained normal since Thus study indicates that chronic renal hypertension in man as in the rat can be reversed when abnormal renal tissue is excised and a normal kidney is given a normal blood supply The similarity of the results of experiments in rats and this study in man at least gives some hope that experimental renal hypertension in animals bears some relation to human disease

Let u consider again the contrast between the persistence of hypertension following total nephrectomy and the restoration of blood pre sure to normal when the clip is removed (Fig 1 Curves A and B) This result does not support the view that hypertension is caused by a renal pressor substance but is compatible with the hypothesis that a normal kidney does something to maintain normal blood pressure and that when the kidney is rendered abnormal by renal artery constriction this function is lost and the blood pressure is raised by factors outside the kidney we can call these factors collectively the extra renal pressor mechanism This would explain why sub equent removal of the kidney doe not affect the blood pressure whereas restoration of normal circulation restores the function of the kidney to maintain normal blood pressure If this is true we would expect that total nephrectomy in normal animals would result in hypertension GROLLMAN (1949) and others have

demonstrated that this does indeed occur and we have confirmed their results Curve C in Fig 1 shows the mean blood pressure of a group of normal rats following consecutive removal of the kidneys five days after total nephrectomy considerable hypertension develops LEDINGHAM (1951) has produced hypertension for up to 6 weeks duration in the nephrectomised member of a pair of parabiotic rats and has coined the term renoprival hypertension

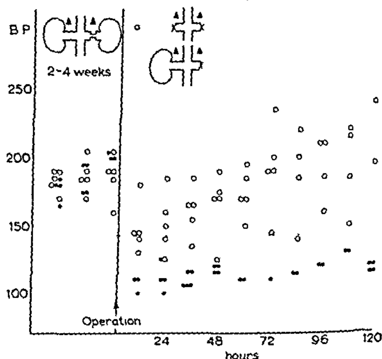


Fig 3 Comparison of the effect of bilateral nephrectomy (O) with that of removal of the clipped kidney ( ) in rats with 2-4 weeks hypertension (Reproduced by kind permission of the Editor of the Ciba Foundation Symposium on Hypertension 1954)

The result of these three experiments suggest that in the chronic stage of renal hypertension the kidney is failing to perform some function which maintains normal blood pressure and that other factors which we will collectively call the extra renal pressor mechanism can then raise the blood pressure The most obvious objection to this hypothesis is the fact that in the rat and in man a single abnormal kidney can cause hypertension we must ask why the normal remaining kidney does not maintain normal blood pressure since removal of one kidney does not cause hypertension At first sight this might appear to be evidence for the existence of a renal

pressor mechanism but this possibility is excluded by our finding (FLOYER 1954) that removal of both kidneys in a rat with hypertension of 2-4 weeks duration produced by constriction of one renal artery without removal of the opposite kidney, fails to restore the blood pressure to normal (Fig 2 circles) In contrast, removal of the clipped kidney alone in similar animals restores the blood pressure to normal in a few hours (Fig 2 dots) This suggests that constriction of one renal artery produces a temporary change in function of the opposite untouched kidney so that the latter behaves like a clipped kidney and does not prevent the blood pressure from rising When the clipped kidney is removed provided that the untouched kidney has suffered no vascular damage the untouched kidney resumes normal function and is able to restore the blood pressure to normal

This effect of one kidney on the function of the other might be brought about by a humoral agent or by the sympathetic nervous system Destruction of the sympathetic nerve supply to both kidneys by stripping the renal pedicles does not prevent the development of hypertension after clipping one renal artery so it is possible that the clipped kidney secretes a substance which causes a temporary change in function in the opposite untouched kidney The results of all our animal experiments and also the observations of Merrill on his patient with a transplanted kidney are in keeping with this hypothesi

We must now ask what is the nature of the extrarenal pressor mechanism and how the normal kidney maintains normal blood pressure The normal kidney might secrete a depressor substance it might destroy or excrete a pressor substance secreted by another organ or it might control by internal regulation the level in the blood of various substances which affect the peripheral blood vessels and so maintain constant the tone reactivity or the actual size of the smooth muscle cells in the arterioles thereby maintaining normal peripheral resistance I have only one more piece of evidence which is that the part played by the kidney in the maintenance of blood pressure is independent of its power to excrete GROLLMAN (1949) has demonstrated that whereas removal of both kidneys in dogs results in hypertension removal of one kidney and implantation of the ureter of the other into the inferior vena cava does not cause a rise in blood pressure We have confirmed these results in rats (FLOYER 1955) In a series of rats one kidney was removed and the opposite ureter was implanted into the inferior vena cava These rats were maintained alive by peritoneal dialysis The blood urea rose to a level

similar to that seen after removal of both kidneys but provided that the kidney did not become dilated the blood pressure remained normal This suggests that a structurally intact kidney even though not excreting, can maintain normal blood pressure We have also shown that removal of the constricting clip and simultaneous implantation of the ureter into the vena cava restores the blood pressure to normal, indicating that a normal kidney can restore the blood pressure to normal even though it is not excreting

In conclusion, it appears that in experimental renal hypertension a state is reached soon after renal artery constriction in which total nephrectomy fails to reverse the hypertension, this occurs whether or not the opposite or untouched kidney is removed In animals with two kidneys removal of the clipped kidney alone restores the blood pressure to normal provided that the untouched kidney is intact but if this kidney has suffered hypertensive vascular damage *the blood pressure remains elevated following* excision of the clipped kidney The hypertension is always reversible however when the constricting clip is removed and normal circulation is restored to a normal kidney and the damaged untouched kidney, if present is removed The hypothesis which explains these results best is that the normal kidney in some manner maintains normal blood pressure when the kidney is rendered abnormal or is excised this function is lost and some mechanism is allowed to raise the blood pressure Restoration of normal circulation to the kidney however appears to inhibit this mechanism and to restore normal blood pressure no permanent change occurs in the circulation which severs the hypertension from renal control This renal control of blood pressure is exercised through some internal metabolic function of the kidney and does not depend upon the power of the latter *to excrete*

REFERENCES

BLACKET R B and SELLERS A L (1951) *Clin Sci* 10 177
BYROM F B and DODSON L F (1949) *Clin Sci* 8 1
FLOYER M A (1951) *Clin Sci* 10 417
FLOYER M A (1954) *Ciba Symposium on Hypertension* Churchill London p 155
FLOYER M A (1955) *Clin Sci* 14 163
GOLDBLATT H LYNCH J HANZAL R F and SUMMERVILLE W W (1934) *J exp Med* 59 347
GROLLMAN A MUIRHEAD E E and VANATTA J (1949) *Amer J Physiol* 157 21
HAYNES F W and DEXTER L (1947) *Amer J Physiol* 150 190
LEDINGHAM J M (1951) *Clin Sci* 10 423
MERRILL J P MURRAY J E HARRISON J H and GUILD W R (1956) *J Amer med ass* 160 277
PICKERING G W (1945) *Clin Sci* 5 229
WILSON C and BYROM F B (1939) *Lancet* i 136

EXTRARENAL FACTORS IN THE PATHOGENESIS OF HYPERTENSION

J M LEDINGHAM

PROFESSOR WILSON and Dr FLOYER have outlined the experiments which have led to the concept of an extrarenal pressor mechanism in the pathogenesis of experimental renal hypertension and shown evidence for the belief that this mechanism is closely related to that which underlies renoprival hypertension My purpose is to discuss what is known of the possible factors involved in this extrarenal pressor mechanism It was natural first of all to consider the impor tance of the adrenal cortex and of electrolytes in this respect The adrenal cortex is now well recognized to be necessary for the main tenance of the normal blood pressure Adrenal cortical failure is associated with a fall in blood pressure not always accompanied by hyponatraemia and haemoconcentration and therefore not directly attributable to a diminution of blood volume (KNOWLTON 1953 SWINGLE *et al* 1954) This would suggest that adrenal cortical factors have some direct influence on arteriolar tone That this influence is at least partly exerted through the adrenal cortical control of electrolyte distribution is clear from the fact that the circulatory disturbances in adrenal insufficiency can be diminished by the replacement of sodium lost in the urine Available information con cerning the relationship of the adrenal to various forms of hyper tension is presented in Table 1 In this table are included two other forms of experimental hypertension not yet mentioned which are of immediate relevance in this discussion that is salt hypertension and steroid hypertension It will be seen that the adrenal is necessary for the maintenance of experimental renal hypertension and reno prival hypertension but can be substituted in this respect at least partially by sodium (FLOYER 1951) Both deoxycortone and corti sone are pressor in the absence of the adrenals and under these circumstances sodium potentiates the pressor action of deoxycortone and depresses that of cortisone (KNOWLTON *et al* 1952 LEDINGHAM 1954b)

The problem posed is whether the action of the adrenal cortex

Table 1

	Type of experimental hypertension				
	Experimental renal	Renoprival	Deoxycortone	Cortisone	Salt
Adrenalectomy	Development of H T inhibited and H T already present abolished	Development of H T inhibited	Nil	Nil	Development of H T inhibited but H T already present partially maintained
Na substitution after adrenalectomy	Development of H T still inhibited but H T already present partially maintained	H T develops	—	(H T inversely correlated with Na intake)	—
Na intake increased	Slightly pressor	Pressor	Pressor	Nil	—
Na intake decreased	Depressor when Na intake greatly reduced	Depressor	Depressor	Nil	—

The behaviour of various types of experimental hypertension in relation to adrenalectomy and to the intake of sodium

or of the sodium ion) in the maintenance of experimental renal hypertension and renoprival hypertension is merely permissive or directly causative In other words is the adrenal required purely to maintain a basic arteriolar tone on which some other pressor factor exerts its action or is the adrenal more directly implicated in the extrarenal pressor mechanism? This is a very vexed problem and the only evidence we have which bears on it is that from the study of hypertension in parabiotic rats (LEDINGHAM 1951) (Fig 1) From

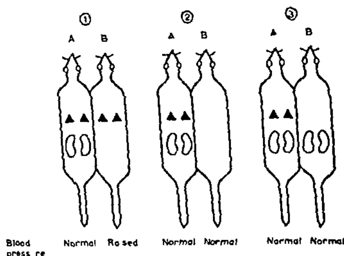


Fig 1 The blood pressures in the two members of a parabiotic pair of rats one member of the pair (Rat B) being subjected to various operative procedures including nephrectomy and adrenalectomy

these experiments we must conclude that in the hypertensive nephrectomized parabiont a greater quantity of adrenal factor or factors are required to maintain the hypertension than are required to maintain the basic arteriolar tone in the normotensive adrenalectomized nephrectomized parabiont We have further evidence that experimental renal hypertension induced in one member of a parabiotic pair is also dependent on the presence of the adrenal (LEDINGHAM 1955) (Fig 2) Thus it would appear that more of circulating adrenal factors are required to maintain hypertension than to maintain the normal blood pressure and suggests that they may be directly concerned in the extrarenal pressor mechanism This tentative conclusion does not mean that the adrenal is necessarily producing more of these factors in experimental renal hypertension and renoprival

hypertension, but simply that the factors are more readily available in the circulation This concept is outlined schematically in Fig 3

The knowledge that sodium chloride is intimately bound up with the production and maintenance of various forms of hypertension has naturally led to the investigation of disturbances of body water and electrolytes in these conditions Studies of this kind have met

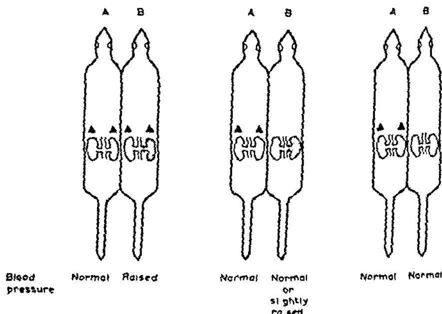


Fig 2 The blood pressures in the two members of a parabiotic pair of rats Experimental renal hypertension was induced in one member (Rat *B*) by the application of a clip to one renal artery Subsequently adrenalectomy was performed on this member

with at least two obstacles In the first place it was soon found that changes in the extracellular compartment of the body fluids were not an essential concomitant of the hypertensive state Thus in experimental renal hypertension the concentration of cations in extracellular fluid may be normal and the volume of the extracellular fluid may be normal also (LEDINGHAM 1953) Renoprival hypertension more readily occurs if the extracellular fluid is allowed to expand through the administration of saline (BRAUN MENENDEZ and COVIAN 1948) though it has been shown that it may arise in the absence of such expansion (MUIRHEAD *et al* 1953) furthermore the extracellular cation concentration may be normal although there is a loose correlation between the level of sodium and the hypertension

(KOLFF *et al* 1954) Hence electrolyte disturbances if they exist at all in hypertension must be in the intracellular compartment Herewith arises the first difficulty Studies of the changes in body water and electrolytes embracing the intra and extracellular spaces as a whole are unrewarding Specific tissues vary widely in their composition of intracellular el ctrolytes and in the freedom with which the electro lyte concentrations alter under different circumstances Therefore studies must be made in various sites including the heart and blood

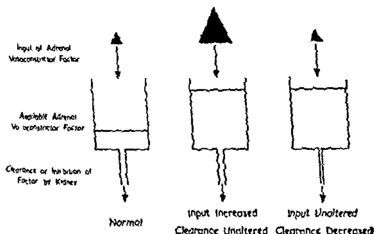


Fig 3 Schematic representation of *two possible* ways in which the availability of a hypothetical adrenal vasoconstrictor factor *might* be al ered

vessels It would be logical to include the *arterioles* in these studies but their size precludes this In the second place techniques for defining the extracellular space are the subject of much controversy The common practice of using the chloride space for this purpose is particularly open to criticism The use of inulin is less objectionable Reports from various laboratories on the electrolyte disturbances in experimental renal hypertension are rather at variance due at least in part to the various chemical methods and also to the different techniques employed to interfere with the renal circulation Inter ference with the kidneys such as simple unilateral nephrectomy produces disturbances in the extracellular fluid volume and opera tions on the sole remaining kidney may induce further disturbances possibly involving intracellular electrolytes unaccompanied by hypertension (LEDINGHAM 1953 TOBIAN and BINION 1954) Hence

interpretation of the significance of observed changes becomes extremely difficult

Our own studies (LEDINGHAM 1953 1954a and b) using inulin to define the extracellular space have been confined to the water and electrolyte disturbances in heart and skeletal muscle taking place in various forms of experimental hypertension In experimental renal hypertension the changes if they exist at all are small Some evidence was obtained for a reduction in the intracellular concentration of

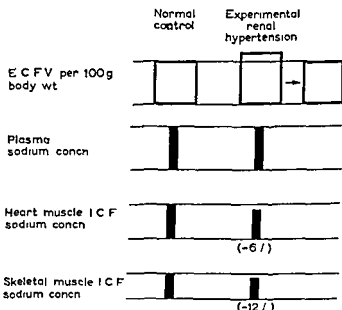


Fig 4 Changes in the extracellular fluid volume (e c f v) and the concentration of sodium in the plasma and the intracellular fluid (i c f) of heart and skeletal muscle in experimental renal hypertension in rats

sodium in heart and skeletal muscle (Fig 4) After total nephrectomy we have evidence that the adrenals cause withdrawal of sodium from the intracellular compartment in heart and skeletal muscle and thereby bring about a reduction in the intracellular sodium concentration (Fig 5) It is under these circumstances that renoprival hypertension occurs Studies of the changes occurring in hypertension following the administration of cortisone and deoxycortone are more complex in view of the many variables involved but here again there is some evidence that hypertension is associated with an increase of extracellular relative to intracellular sodium in heart muscle

Our conclusions up to this point are therefore that greater quantities of circulating adrenal pressor factors are likely to be found in

experimental renal hypertension and in renoprival hypertension and that these may possibly exert their pressor action through their influence on the electrolyte distribution in the heart and blood vessels Further studies along these lines are urgently needed

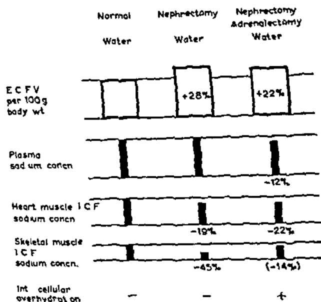


Fig. 5 Changes in the extracellular fluid volume (e c f v) and the concentration of sodium in the plasma and *intracellular* fluid (i c f) of heart and skeletal muscle in rats following total nephrectomy or total nephrectomy and adrenalectomy with the provision of drinking water after operation

Lastly we must consider how these hypothetical pressor factors might operate in the production of hypertension Various possibilities are discussed below

1 Firstly these factors may sensitize the arterioles to normally circulating pressor agents of nonrenal origin known or unknown Much work has been directed to the vascular reactivity to adrenaline noradrenaline and other pressor substances in adrenalectomized animals both untreated and treated with adrenal steroids Various experimental techniques have been employed Using the blood pressure response itself as an indication of reactivity it has been found that in advanced adrenal insufficiency this response is depressed (RAMEY *et al* 1951 SALMOIRAGHI and MCCUBBIN 1954) but is maintained after treatment with adrenal cortical steroids (RAMEY

et al, 1951) However, the initial blood pressure in the adrenal insufficient animal is in general lower than in the normal control and the significance of differences between blood pressure elevations under these circumstances is uncertain Furthermore differences cannot be attributed necessarily to differences in vascular reactivity but rather to differences in reactivity of the cardio vascular system taken as a whole Recently studies of the blood flow through the peripheral vascular bed in adrenal insufficient dogs (BROWN and REMINGTON 1955) have failed to demonstrate any decrease in responsiveness On the other hand using the rat mesoappendix preparation the vessels were found to be refractory to topical noradrenalin after adrenalectomy responsiveness being restored by the topical application of adrenal cortical extracts (FRITZ and LEVINE 1951) As regards the possibility of enhancing responsiveness to various pressor agents by the administration of adrenal cortical steroids to man or to intact animals there is as yet no agreement Observations in rats and dogs revealed no increase in the blood pressure response to adrenaline renin, and angiotonin after treat ment with deoxycortone (MASSON *et al*, 1950) and in dogs no increased response was observed after the acute injection of adrenal cortical extracts (RAMEY *et al* 1951) Using the rabbit ear chamber technique no increased sensitivity to noradrenaline was observed after cortisone (WILLIAMS *et al* 1954) On the other hand in man an increased blood pressure response to infusions of adrenaline and nor adrenaline was reported after treatment with deoxycortone (RAAB *et al* 1950) In conclusion it must be admitted that this first possibility cannot be substantiated in the light of available evidence

2 Secondly These factors may have a direct action on arteriolar tone themselves We have no conclusive evidence for or against this view

The results which Dr FOLKOW reports are superficially in opposi tion to these first two possibilities There are some comments which we should like to make in this context In the first place his material is from human cases of long standing hypertension in whom the complicating factor of atheroma in the larger arteries arises Atheroma is accepted to be accentuated by hypertension and is a well recognized cause for reduction in blood flow through the peripheries Experimental renal hypertension induced in young rats is not complicated in this way and there is no doubt that long standing hypertension of renal origin is quickly reversible (BYROM and DODSON 1949) as is also renoprival hypertension by kidney

grafung (KOLFF and PAGE 1954) These observations strongly oppose a concept of structural change In the second place Dr FOLKOW considers that the smooth muscle cells in the arterioles are completely relaxed by his treatment of the arm This may be so but it is still possible that the shape of the relaxed muscle cell is different from normal by reason for instance of changes in its electrolyte content This interpretation would permit a reconciliation with our own experience of the rapid reversibility of hypertension In the third place we question whether it is justifiable to consider that myogenic tone sympathetic tone etc are strictly summated on this basal relaxed state

3 Thirdly These adrenal pressor factors may not after all act upon the arterioles but upon the heart The concept of local myogenic activity first suggested by BAYLISS (1902) by which the smooth muscle of arteriolar wall reacts to an increase of intravascular pressure by vasoconstriction has received strong support from the work of Dr FOLKOW (1949 1952) This idea opens up the possibility that more forcible contraction of the heart is primary in the genesis of hypertension and that the vasoconstriction of the vessels is secondary to this and mediated through the local myogenic activity The testing of such a possibility presents physiologists with a most complex haemodynamic problem

Finally we should say that in the study of the cause of hypertension the search for a circulating vasoconstrictor substance in the usual s nse of the word may be fruitless Furthermore it is in the bounds of possibility that *no* alteration may be found in the normal function of the vessels at all but rather in the heart We are indeed still very far away from the full understanding of this diffi ult problem

REFERENCES

BAYLISS W M (1902) *J Phys* 28 220
BRAUN MENENDEZ E. and COVIAN M R (1948) *Rev Soc argent Biol* 24 130
BROWN F K and REMINGTON J W (1955) *Amer J Phys* 182 279
BRYOM F B and DODSON C F (1949) Clin Sci 8 1
FLOYER M A (1951) *Clin Sci* 10 405
FOLKOW B (1949) *A ta physiol s and* 17 289
FOLKOW B (1952 53) *Acta physiol scand* 27 99
FRITZ I and LEVINE R (1951) *Amer J Phys* 165 456
KNOWLTON A I LOEB E N STOERK H C WHITE J P and HEFFERMAN J F (1952) *J exp Med* 96 187
KNOWLTON A I (1953) *Amer J Med* 15 771
KOLFF W J and PAGE I H (1954) *Amer J Physiol* 178 75
KOLFF W J PAGE I H and CORCORAN A C (1954) *Amer J Physiol* 178 237
LEDINGHAM J M (1951) *Clin Sci* 10 423
LEDINGHAM J M (1953 *Clin Sci* 12 337

LEDINGHAM J M (1954a) *Clin Sci* 13 535
LEDINGHAM J M (1954b) *Clin Sci* 13 543
LEDINGHAM J M (1955) Unpublished observations
MASSON G M C PAGE I H and CORCORAN A C (1950) *Proc Soc exp Biol N Y* 73 434
MUIRHEAD E E JONES M S and GRAHAM P (1953) *Circulation Res* 1 439
RAAB W HUMPHREYS R J and LEPESCHKIN E (1950) *J clin Invest* 29 1397
RAMEY E R GOLDSTEIN M S and LEVINE R (1951) *Amer J Phys* 165 450
SALMOIRAGHI G C and McCUBBIN J W (1954) *Circulation Res* 2 280
SWINGLE W W BEN M MAXWELL R BAKER C FEDOR E and BARLOW G (1954) *Endocrinology* 54 698
TOBIAN E and BINION J (1954) *Amer J Phys* 178 233
WILLIAMS C O HEIPLE K G and EBERT R H (1954) *J Lab clin Med* 44 210

DISCUSSION PAPERS

THE PHYSIOLOGICAL RESPONSE TO NITRO-GLYCERINE IN NORMAL AND HYPERTENSIVE RABBITS

JAMES CONWAY

HYPERTENSION is particularly interesting for the physiologist because it is a theoretically impossible condition On the one hand there are complicated processes increasing peripheral resistance and raising blood pressure and on the other there is a well established system of homeostatic reflexes based on the carotid sinus and aortic stretch receptors apparently ignoring it As the blood pressure rises at no stage does one see a period of bradycardia to indicate the onset of reflex activity and yet from the work of VERNEY and VOGT (1938) GOLDBLATT *et al* (1940) PICKERING *et al* (1936) and others it is known that the carotid sinus reflexes remain active in the presence of hypertension and could depress the blood pressure Recent electro physiological studies by McCUBBIN GREEN and PAGE (1956) have shown that the baroreceptors in the carotid sinuses themselves appear to be set higher and to operate about the hypertensive levels

Since the effectiveness of the control of blood pressure in hyper tension is of some practical importance experiments have been performed to test indirectly the efficiency of the regulative reflexes

An injection of nitroglycerine into the marginal vein of the ear of a conscious normotensive rabbit leads to a depression of the blood pressure and its rapid restoration in 10–20 sec depending upon the dose (Fig 1) After injections of very large doses of hexamethonium 60–80 mg in divided doses injections of nitro glycerine can be repeated from more or less the same initial level of pressure but with little interference from the reflexes

As far as pressure regulation is concerned there are two points of interest in these responses to nitroglycerine the onset of tachy cardia and the restoration of pressure to normal

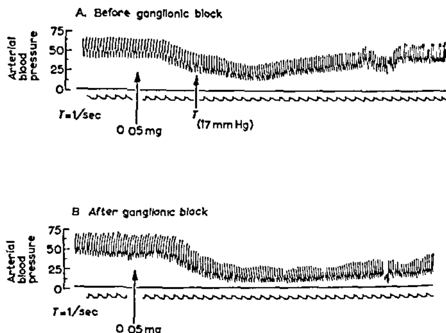


Fig 1 The effect of injections of nitroglycerine in the conscious rabbit before and after the administration of hexamethonium (60 mg) The blood pressure was recorded directly from the central artery of the ear by a condenser manometer *T*=indicates the point at which reflex tachycardia appeared

(1) The level at which tachycardia appears indicates the deviation from the resting level of pressure which can occur before the reflex is excited and from Fig 1 it can be seen that the fall in blood pressure is temporarily arrested at this point

(2) The return of pressure is produced reflexly By comparing the response to nitroglycerine before and after hexamethonium it can be seen that the reflex restoration of pressure occurs at a time when the response after hexamethonium shows the dilator effect of the drug to be fully active

Repeated experiments of this kind have been performed on 5 rabbits in their normal state and again after producing hypertension by perinephric fibrosis the pattern of the response was unchanged with the development of hypertension In repeated tests the mean fall in blood pressure after which tachycardia appeared following a dose of 50 μg of nitroglycerine was 12 mm Hg in the normal and 15 mm Hg in the hypertensive The mean duration of the effect before ganglion block was 22 sec in normals and 21 in hypertensives

The reflex response to a rise in blood pressure was also assessed from injections of noradrenaline (1 25 µg) before and after hexa methonium The onset of bradycardia and the restoration of blood pressure within half a minute indicated the activity of the depressor reflex Again the behaviour of the hypertensive animal was indis tinguishable from the normal (CONWAY 1955)

These experiments show indirectly that the regulating reflexes lose none of their efficiency with the development of hypertension

Two points of practical interest arise from this work The first is that any therapeutic attempt to reduce the blood pressure in hypertension will be resisted by these powerful homeostatic reflexes and it seems that a therapeutic approach to severe hypertension might be made by utilizing the methonium compounds to block the restora tive reflexes while a vasodilator agent—perhaps a long acting nitrite —is used to relax arterial muscle directly

The second point is of interest in view of what Dr FOLKOW has said about the inability of the forearm vessels to dilate in hyper tension The ability of nitrites to reduce the blood pressure has been studi d in 8 rabbits on different occasions in their normal state

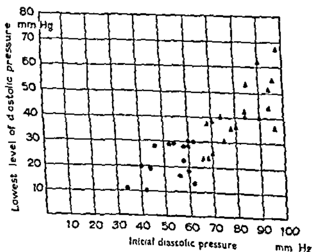


Fig 2 Depression of the blood pressure by supramaximal doses of nitroglycerine (25–100 µg) after hexamethonium
Repeated experiments were performed on 8 rabbits
● in their normal state
▲ after operation for the production of hypertension by perinephric fibrosis

and again after the production of hypertension by perinephric fibrosis

With the development of hypertension (Fig 2) the masimal reduction of blood pressure achieved by nitroglycerine became progressively limited roughly in proportion to the severity of the hypertension

While the conclusions that can be drawn from experiments of this kind are necessarily limited they do support the contention that something other than vascular spasm must be responsible for the increased peripheral resistance in hypertension

REFERENCES

CONWAY J (1955) *Clin Sci* 14 625

GOLDBLATT H KAHN J R BAYLEES F and SIMON M A (1940) *J Exp Med* 71 175

MCCUBBIN J W GREEN J H and PAGE I H (1956) *Circulation Research* 4 205

PICKERING G W KISSIN M and ROTHSCHILD P (1936) *Clin Sci* 2 193

VERNEY E B and VOGT M (1938) *Quart J exp Physiol* 28 253

SOME CHARACTERISTICS OF PERIPHERAL ARTERIOLES IN HUMAN HYPERTENSION

ROBERT S DUFF

THERE is unfortunately a slight difference between wild animals more or less eviscerated and human beings more or less civilized

Chronic arterial hypertension results from a widespread reduction in the calibre of arterioles of the systemic vasculature Investigation of the peripheral circulation in man may therefore provide a direct approach to the understanding of the nature of human hypertension The following observations are derived from an enquiry into the functional state of arterioles of the hand in patients with high blood pressure contrasted with healthy subjects

Three studies of these vessels have been made to determine (1) their mean calibre before and after treatment (2) their response to directly applied chemical stimuli and (3) the influence of cortisone on vascular reactions

The normal subjects comprised altogether 60 healthy adults most of whom were medical student volunteers Many of these were

investigated in Prof HENRY BARCROFT s Department at St Thomas s Hospital with the collaboration of Dr JEAN GINSBURG At St Bartholomew s Hospital by courtesy of Dr GEOFFREY BOURNE and Dr GRAHAM HAYWARD more than 30 hypertensive patients have been studied so far

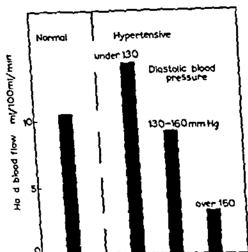


Fig 1 Mean resting blood flow in the hands of groups of healthy and hyper tensive subjects the latter are graded according to the level of diastolic arterial pressure (From DUFF 1956)

In every test the blood flow in the hands was measured by venous occlusion plethysmography under standard conditions (DUFF 1952 BARCROFT and SWAN 1953)

The hand blood flow at rest of members of a fairly large group of healthy subjects extended over a very wide range but averaged 10 5 ml/minute/100 ml hand volume In patients with high blood pressure the flow varied with an overall range like that of the normals and with a mean value not significantly different from the normal group (Fig 1) But when the hypertensive patients were grouped according to their diastolic blood pressures two further facts emerged The first was that the blood flow tended to be inversely related to the arterial pressure the second was that in the least severe group (with diastolic blood pressures between 100 and 130 mm Hg) the hand blood flow was actually greater than normal This finding is of interest, for it suggests that in hypertension the

vascular narrowing though widespread, does not in the early stages involve the vessels of the hand

After treatment with hexamethonium (and related drugs) the resting level of flow in the hands was consistently lowered (Fig 2) No doubt this was partly the result of the reduction in arterial pressure in the upper half of the body by the hexamethonium However the fall in blood flow was usually greater than the fall in blood pressure

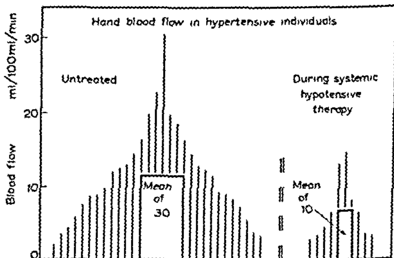


Fig 2 Resting hand blood flow in untreated hypertensive patients compared with patients in whom the blood pressure has been reduced by hexamethonium

It is likely therefore that hexamethonium diverts blood into tissues other than the hands The blood flow in the feet and legs is known to be increased by the systemic administration of this drug (HAMILTON, HENLEY and MORRISON 1954) The lowering of blood pressure by hexamethonium may therefore be the result of an action on the autonomic nervous system producing a more or less selective relaxation of those blood vessels mainly responsible for the peripheral resistance

The second investigation concerned the response of arterioles of the hand to the constrictor effects of adrenaline and noradrenaline These hormones were infused unilaterally into the brachial artery in physiological amounts at rates of between 1 64 and 1/8 microgramme per minute These doses were small enough to produce effects confined to the infused hand The results were analysed to

assess changes in blood flow due solely to the local action of each substance on the peripheral arterioles

In the first series the effects of adrenaline were measured in hypertensive and in healthy subjects When the mean responses of the 2 groups were compared (Fig 3) it was obvious that with each dose of adrenaline the hypertensives exhibited more vasoconstriction

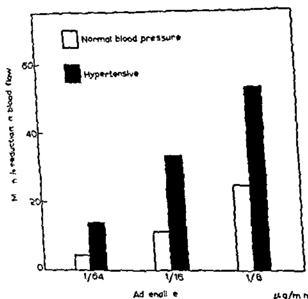


Fig 3 Mean constrictor responses of groups of healthy (clear rectangles) and hypertensive (black rectangles) subjects to intra arterial infusions of adrenaline 1/64 1/16 and 1/8 μg minute (From DUFF 1956b)

than the normals Three obvious explanations for this suggested themselves It might be (1) a physical consequence of vascular narrowing or (2) the result of actual hypertrophy of the smooth muscle of the arteriolar sphincters or else (3) a specific change in the chemical susceptibility of the arterioles

Vascular narrowing could hardly be responsible for there was no precise relationship between the level of flow and the response to adrenaline (Fig 4) This was so not only for the hypertensives but al o for a fairly large group of healthy subjects If anything the subjects with a low resting blood flow had a comparatively small—not large—response to adrenaline

Fig 4 Adrenaline vasoconstriction in healthy subjects grouped according to *the resting level of flow in the hands* The response to *adrenaline 1 8 µg min* bears no precise relationship to the resting flow and is certainly not increased in those with low resting flows

Fig 5 Mean response of the blood vessels *of the* hand to *adrenaline of hyper*tensive *individuals* graded according to the severity of the disease showing the *increased responses* of the majority especially those with more severe grades of hypertension (From DUFF 1956b)

The second possibility attributed the increased reaction of hypertensives to hypertrophy of the arteriolar sphincter muscle Fig 5 shows the adrenaline responses of hypertensive individuals Patients with no evidence of vascular damage in the retinae heart or kidneys are indicated by clear rectangles those with malignant hypertension by black rectangles and those with vascular lesions

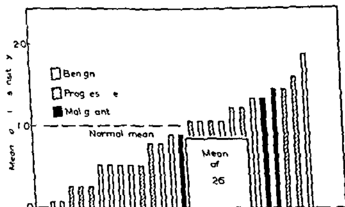


Fig 6 Mean responses of hypertensive individuals to noradrenaline The responses of the majority fall within the range of a group of healthy subjects indicated by the dotted line

of intermediate severity by shaded rectangles In most of these patients the adrenaline responses were greater than the normal which is shown by the dotted line Increased adrenaline vasoconstriction was in general related to the severity of the hypertension

But if the increased vascular reactions were simply an expression of hypertrophy of the smooth muscle of the arterioles then a similar enhancement of the response to other constrictor stimuli should be demonstrable Fig 6 however shows that when the same hypertensive patients were tested in identical manner with noradrenaline most of them were not more reactive than normal to the peripheral vascular effects of the latter drug

It therefore seems likely that the increased adrenaline response in hypertension is a specific chemical change in the smooth muscle of the terminal arterioles

Systemic treatment with hexamethonium resulted in an interesting change in these responses (Fig 7) The sensitivity to adrenaline was not greatly altered but that to noradrenaline was markedly

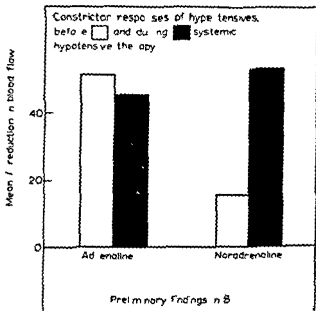


Fig 7 Constrictor responses of hypertensive patients before (clear rectangles) and during (black rectangles) systemic treatment with hexamethonium The latter results in increased sensitivity to noradrenaline

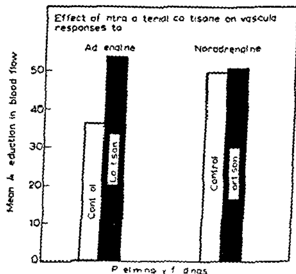


Fig 8 Effect of cortisone on direct responses of the vessels of the hand to adrenaline and to noradrenaline In a preliminary series of 8 normal subjects an increased sensitivity to adrenaline was found an effect resembling that present in essential hypertension

increased This is further evidence that the arteriolar effectors (or should one say receptors?) respond differently to the two adrenergic hormones

Attempts are now being made to unravel the mechanism of this increased sensitivity to adrenaline in hypertensive patients

Since high blood pressure is a disease of civilization then possibly there is a derangement of the system involved in the reaction of the body to stress It seemed reasonable therefore to examine the influence of the suprarenal cortex on vascular reactions To get some indication of this the peripheral responses to intra arterial adrenaline and to noradrenaline have been tested before and after infusing small amounts of a preparation of cortisone into the brachial artery of normal subjects

Preliminary findings suggest that cortisone may enhance the r sponse of vessels of the hand to adrenaline but not to noradrenaline (Fig 8) If confirmed then this is evidence that the suprarenal cortex may be involved in essential hypertension for the previous study indicated an increase in vascular sensitivity specifically to adrenaline in patients with high blood pressure

SUMMARY

(1) Studies of the blood flow in the hands of patients with high blood pressure indicate that in the early stages the vasoconstriction does not involve the vessels in these extremities

(2) In the treatment of hypertension hexamethonium seems to be particularly effective on that portion of the vascular tree mainly responsible for the increased resistance

(3) In the hands of patients with high blood pressure there is evidence of a specific increase in the sensitivity of the vessels to adrenaline

(4) Hexamethonium does not appear to alter this though it does cause hypersensitivity to noradrenaline

(5) Preliminary studies suggest that in high blood pressure the suprarenal cortex may be involved in the disturbed response of the vessels to the adrenergic hormones

REFFRENCES

BARCROFT H and SWAN H J C (1953) *Monographs of the Physiological Society* No 1 Arnold
DUFF R S (1952) *J Physiol* 117 415
DUFF R S (1956a) *Brit Med J* (in the press)
DUFF R S (1956b) *Brit Heart J* (in the press)
HAMILTON M HENLEY K S and MORRISON B (1954) *Clin Sci* 13 225

THE CONTROL OF VASOMOTOR TONE IN HYPERTENSION

W S PEART

IT seems fairly clear that most forms of hypertension are due to an increase in the peripheral resistance and that other factors such as cardiac output and blood viscosity are usually normal (PICKERING 1936a PICKERING, 1955) The distribution of blood flow has not been completely studied but some measurements suggest an increase in muscle blood flow in patients with hypertension (ABRAMSON and FIERST 1942) and a decrease in renal blood flow in some cases (GOLDRING *et al*, 1941)

INCREASED PERIPHERAL RESISTANCE

In investigating the nature of the increased peripheral resistance we have measured the blood flow in the hand by means of calorimetry (GREENFIELD and SCARBOROUGH 1949) and comparisons of the so called maximum heat elimination after warming the other arm or legs have been made This method gives quite reproducible results from day to day in the same subjects and it does seem that vasoconstrictor tone is removed completely since no further increase occurs if the nerves to the hand are anaesthetized (PICKERING 1936a) However it must be mentioned that RODDIE and SHEPHERD (1956) have shown by venous occlusion plethysmography that the blood flow can rise still higher if local heating is combined with heating of the other limbs Therefore what we have measured is presumably not the maximum vasodilatation possible but represents the hand blood flow when sympathetic tone is eliminated Under these conditions a rise of arterial pressure should be accompanied by a rise of hand flow unless the hand is the site of the increased peripheral resistance This is illustrated by the effect on the maximum heat elimination of closing a large femoral arteriovenous fistula in a patient Occluding the femoral artery proximal to the fistula raised the blood pressure and the maximum heat elimination (PICKERING 1936a)

The results we have obtained relevant to the nature of the peripheral resistance in various forms of hypertension are as follows

(1) In essential hypertension the maximum heat elimination is well within the normal range It seems therefore that increased arterial pressure is balanced by increased peripheral resistance in the hand and that there is no evidence of increased vasomotor tone (PICKERING 1936a STEAD and KUNKEL 1940 MENDLOWITZ and TOUROFF 1952)

(2) In chronic nephritis with hypertension the maximum heat elimination is within the normal range

(3) In CUSHING s syndrome with hypertension the maximum heat elimination was normal in two cases In one case removal of a malignant adrenal tumour led to a fall of arterial pressure to normal levels and the maximum heat elimination fell to rise again to its previous levels with the development of metastases and a return of the blood pressure to high levels The non nervous increase in peripheral resistance therefore remained relatively unaltered in the face of a changing blood pressure

(4) In acute nephritis during the phase of hypertension *maximum* heat elimination is in the upper normal range or above it Moreover as arterial pressure falls so does the maximum heat elimination (PICKERING 1936b) Cardiac output is not particularly *increa ed* (DAVIES 1951) and it can be concluded that there is no evidence for any non nervous vasoconstriction in the hand in contrast to chronic nephritis and essential hypertension (see also ARNOTT and MATTHEW 1939)

(5) In phaeochromocytoma the maximum heat elimination is usually much less than in normal subjects (BARNETT *et al* 1950 HAMILTON *et al* 1953) The reduction is conspicuous during the characteristic attacks in which the pressure rises sharply but it is also reduced in patients with sustained hypertension not subject to obvious attacks (HAMILTON *et al* 1953) Removal of the tumour in four patients was as ociated with a return of the maximum heat elimination to normal levels This applies also to those patients who still had persistently raised blood pressures (BARNETT *et al* 1950 HAMILTON *et al* 1953) We can say with reasonable certainty that the diminished hand flow is due to circulating adrenaline and noradrenaline in this condition

In no other condition is it possible to do more than speculate but with the exception of acute nephritis the persistence of a raised peripheral resistance when the effect of the vasomotor nerves is eliminated rules out a nervous cause It might be due to a humoral factor or a structural change in the resistance vessels

FAILURE TO REVERSE HYPERTENSION BY REMOVAL OF THE SUPPOSED PRIMARY CAUSE

There are a number of observations in man which suggest that chronic hypertension may not be completely reversible if the supposed original cause is removed Thus in patients who seem to have unilateral pyelonephritis removal of the affected kidney more commonly fails to reduce the blood pressure to normal Undetected disease in the opposite kidney is a possibility however More convincing, but not yet conclusive is the evidence from patients with phaeochromocytoma In five cases investigated at St Mary s Hospital (HAMILTON *et al* 1953) three had sustained hypertension and removing the tumour left the pressure elevated in two patients (seen respectively 3½ and 1½ years after operation) even though the urinary excretion of catechol amines returned to normal (PEART, 1954)

Finally CLELAND COUNIHAN and GOODWIN (1956) showed that repair of coarctation of the aorta leaves an arterial pressure which though lower than before is still higher than is normal in patients of the same age and sex

Therefore prolonged hypertension may be accompanied by some change which tends to perpetuate the hypertension after removal of what seems to be the primary cause

REFERENCES

ABRAMSON D I and FIERST S M (1942) *Amer Heart J* 23 84
ARNOTT W M and MATTHEW G D (1939) *Quart J Med N S* 8 353
BARNETT A J BLACKET R B DEPOORTER A E SANDERSON P H and WILSON G M (1950) *Clin Sci* 9 151
CLELAND W P COUNIHAN T B and GOODWIN J F (1956) *Clin Sci* in press
DAVIES C E (1951) *Quart J Med N S* 20 163
GOLDRING W CHASIS H RANGES H A and SMITH H W (1941) *J Clin Invest* 20 637
GREENFIELD A D M and SCARBOROUGH H (1949) *Clin Sci* 8 211
HAMILTON M LITCHFIELD J W PEART W S and SOWRY G S C (1953) *Brit Heart J* 15 241
MENDLOWITZ M and TOUROFF A S W (1952) *Circulation* 5 577
PEART W S (1954) *Ciba Foundation Symposium on Hypertension Humoral and Neurogenic Factors* p 104 London Churchill
PICKERING G W (1936a) *Clin Sci* 2 209
PICKERING G W (1936b) *Clin Sci* 2 363
PICKERING G W (1955) In *High Blood Pressure* London Churchill
RODDIE I C and SHEPHERD J T (1956) *J Physiol* 131 657
STEAD E A Jr and KUNKEL P (1940) *J clin Invest* 19 25

GENERAL DISCUSSION

DR DORNHORST It seems to me that Dr Folkow s interpretation of his findings rests on three assumptions The first is that his relationship of flow and pressure in the completely relaxed vascular system is linear over the whole range That is to say if flow is plotted against pressure in a completely relaxed system this gives a straight line throughout If in fact this is not so but the flow pressure relationship is somewhat curvilinear in the higher pressure range then it may be that the calculated resistance will go up as one is working over higher pressures It may possibly not be justifiable therefore to compare the results in hypertensive cases directly with those in normals

This objection could be met if the effective pressure in the limb were decreased by applying pressure outside the limb It can be done quite simply by lengthening the chimney of the plethysmograph and so increasing the hydrostatic pressure This reduces the effective pressure in the limb and one can get the hypertensive pressure back into the normal range It also of course automatically gets rid of the trouble of the congested veins

The second assumption is that he has in fact achieved maximal vasodilatation by his method of exercising presumably to pain in the ischaemic limb This indeed may be so but I think one has to be rather careful about assuming that full vasodilatation has occurred Our experience with various dilator influences and exercise as well has been that in general it seems almost impossible to saturate the flow so to speak to get really maximal dilatation It would be interesting to repeat some of these experiments after giving a long lasting dilator substance intra arterially It may be that the flow would not go up but I suspect that it would

There is a third assumption and that is that the blood pressure measured in the other arm simultaneously is the local effective blood pressure This assumption is not correct At these high flows there is a drop in local blood pressure It does not amount to very much but it is definitely there If one measures the pressure with a needle in the brachial artery and with an occluding cuff on the arm lower down when that cuff is taken off even with a normal vessel there is a very definite drop after a long period of ischaemia One might think that the drop ought to be the same in normals and in hypertensives but if in fact there is some vasoconstriction in the artery upstream of where the circulation is being occluded *this* might lead to a greater than normal drop in pressure I think one must measure the pressure

where it is effective This is not technically very difficult and it would strengthen the results very much It may very well be that all these objections can be removed by further work, but because this is such a fundamental matter I think they ought to be met

DR FOLKOW As to the first question dealing with the pressure flow relationship of maximally dilated vessels we have performed many experiments on animals and have found that the resistance to flow decreases with increase of pressure in the lower pressure range but at pressures above approximately 100 mm Hg there is an almost linear pressure flow relationship In other words the resistance to flow of the maximally dilated vessels then remains relatively unchanged Burton s explanation of this finding which we also find to be the most reasonable one is that the vascular bed is surrounded by a delicate fibrous network When the maximally dilated vessels are distended by increasing pressures the indistensible network will soon be reached preventing further distention and thus further decrease of resistance when the pressure is raised In the present experiments on man we have assumed that similar relationships hold for the maximally dilated forearm vessels It is in agreement with this assumption that when acute hypertension was induced by nor adrenaline in normotensive subjects their forearm resistance to blood flow at maximal dilatation was not essentially changed Further if the resistance to flow should further decrease due to the raised pressure in acute hypertension the observed difference between normotensive subjects and essential hypertensives should only be more pronounced It is impossible to imagine that for pure physical reasons the pressure flow relationship of *maximally* dilated blood vessels should be concave to the pressure axis in other words that the resistance of the vessels should *increase* when intravascular pressure is raised

It is of course a very important question to know whether the blood vessels were really maximally dilated It is one of the inherent difficulties in this problem Nevertheless our method is as far as we can see the only way by which one can determine whether the vessels in chronic hypertension have an altered architecture with generalized structural changes causing a slight increase in resistance We have tried to increase the dilatation both by increasing the period of ischaemia and by forcing the subjects to work very hard with their ischaemic forearm muscles We were not able however further to increase the forearm blood flow significantly by such procedures In fact we usually found that about 75 per cent of the maximal

obtainable flow was already reached after two minutes of ischaemia and added muscular work and after five minutes of ischaemia about 90 per cent or more was reached In other words the curve correlating the period of ischaemia and muscular work with the peak hyperaemia flattens out after a very steep rise at shorter occlusion periods and there is very little sign of further increase of flow when the ischaemia period and the muscular work is increased further Such a curve can be regarded as a dose response curve correlating the local concentration of vasodilator agents with the vasodilator response The very definite flattening out of this curve suggests at least in our view that the vessels are then at or very near to maximal dilatation

Dr Dornhorst s third question is also quite interesting As far as I can remember Pickering has measured the pressure drop between the brachial artery and the small finger arteries and found this pressure drop to be very small and essentially equal in normotensive and hypertensive subjects under resting conditions Normally therefore th larger arteries contribute very little to the resistance to flow These conditions may however change when a huge dilatation of the resistance vessels is induced as then the great velocity of flow through the larger vessels must magnify the pressure drop along the larger arteries—and also the veins Whether this pressure drop is significantly greater in uncomplicated hypertensive disease is un fortunately not known It does not seem to be so when vascular smooth muscle tone is increased acutely by intravenous infusion of noradrenaline in normotensive subjects Under such circumstances the forearm blood flow at maximal dilatation is in our experience at least increased in proportion to the increased blood pressure as measured from the other forearm Of course it is highly desirable also to measure the blood pressure locally but the factors of stress are so many in this type of experiment that it is often quite difficult to get the patients to co operate Ten minutes vascular occlusion with the forearm in water at 43 C with muscular work added is generally quite uncomfortable

We are well aware of the fact that many pitfalls are involved and for this reason we only want to look at this series of experiments as a suggestion that after all a generalized structural change too small to be easily found by histological techniques may exert a significant influence on the haemodynamics in well-established hypertensive disease Increased vascular smooth muscle tone is not necessarily the only factor involved once blood pressure has been raised for a long period

PROF SMIRK Dr McQueen has been performing some experiments which are related to the question raised by Dr Floyer concerning the relationship between *renoprival hypertension* and clipped kidney hypertension He has been interested in the reactions of blood vessels to noradrenaline taking blood vessels not only from normal rats but from rats which have been hypertensive for various periods of time either as a result of a unilateral clipped kidney a bilateral clipped kidney or a bilateral nephrectomy McQueen finds there is an increased reaction of the perfused blood vessels to noradrenaline This reaction persists during the period of perfusion for quite a period of time for at least twenty minutes or half an hour *of the perfusion period The difference is significant*—at about a one in a thousand level McQueen has made the observation on blood vessels taken from rats with renoprival hypertension and also with clipped kidney hypertension Perhaps the increase in the reactivity of the blood vessels to noradrenaline and possibly to other stimuli is one of the factors which are common to the clipped kidney type of hypertension and to the renoprival type

McQueen also found some degree of increase in reactivity with one clipped kidney and the other kidney present and one wonders whether that means that a substance coming from the kidney may be influencing reactivity as well as a pure renoprival state

PROF WILSON Is this increased reactivity constant in all the forms of experimental renal hypertension and renoprival hypertension? Is it present any more in one than another or does the increased sensitivity apply only to all forms equally?

PROF SMIRK It applies to bilateral nephrectomy and to unilateral *nephrectomy with a clipped kidney* I believe that the degree of enhanced reactivity is approximately the same in the two cases With a unilateral clipped kidney and the other kidney intact and present the degree of increase in reactivity is less

PROF WILSON *Is the difference in reactivity related to the height* of the blood pressure?

PROF SMIRK The increase in the reactivity may occur before the blood pressure actually rises

PROF WILSON I feel that when we talk about increased reactivity we may not really be dealing with an actual increased responsiveness we may be dealing with a normal response in a narrower vessel We

cannot tell whether the vessel is over responsive if the blood pressure is raised so that the lumen of the arteriole is narrowed

PROF SMIRK This is of course a perfused hind quarter of a rat not a whole rat and the finding is present as early as two days after the operative procedure It would require a very exacting form of investigation to prove that there was no hypertrophy in that period of time but it seemed to us that the likelihood of hypertrophy within two or three days after clipping and before the blood pressure actually rose was not a very great one

PROF BURN I wonder whether Dr Ledingham and Dr Floyer have considered this possibility that what happens when the kidney is clipped is that the amine oxidase which is present in the kidney is prevented from working I have learned from Dr Blaschko that in the body there is a great deal of dopamine produced as a result of the action of dopadecarboxylase on dopa This dopamine does not normally have any effect because it is being destroyed by amine oxidase Blaschko has suggested that this is perhaps, one of the main functions of amine oxidase in the body It seems at first sight an obvious possibility that what happens when a kidney is clipped is that the kidney ceases to destroy dopamine the dopamine then causes the hypertension and that hypertension itself may cause the lesions in the opposite kidney

There are two points which one might test Is there in fact any raised excretion of dopamine in the urine of these hypertensive rats? Holtz measured the excretion of dopamine in man and found that it was about 0 3 mg daily whereas the amount of noradrenaline excreted is down at 0 04 mg daily Presumably some dopamine is excreted in the urine of rats also and it might be raised in this clipped kidney hypertension

The other question is whether there is an unusual response in the clipped kidney rats to marsilid a substance which inhibits amine oxidase it might have some striking effect on the blood pressure if there were anything in this hypothesis

I would also like to refer to the question of vascular tone which Dr Folkow discussed I believe that vascular tone returns very quickly after denervation I learnt from Sir Henry Dale a long time ago that if the sciatic nerve is cut the vessels of the hind leg lose their tone at once but it very quickly comes back in a day or two so that there is some mechanism responsible for rapid recovery of tone which is hardly likely to be vascular hypertrophy

As my colleague Dr Kottegoda has shown besides the sympathetic nerves there seems to be a peripheral nervous mechanism of some kind which survives the degeneration of sympathetic fibres and sensory fibres in the ears for example of the rabbit Kottegoda working together with Dr Ginzel showed that in an ear deprived either of its sensory or sympathetic nerve supply if nicotine or acetylcholine was injected the result was constriction That con striction seemed to be due to the liberation of an adrenaline like substance because it could be reversed with tolazoline Without going into details the evidence suggested that there are peripheral nervous mechanisms which may play an important part after denervation

PROF HEYMANS There is another mechanism which must be *considered in any discussion of the control of vascular tone in* hypertension My feeling is that the primary underlying cause of any rise in arterial blood pressure must be a fundamental disturbance in the normal homeostatic mechanism of blood pressure regulation These homeostatic mechanisms are very powerful The aortic and carotid sinus baroceptors are able to counteract any drop in arterial blood pressure and also a rise in arterial blood pressure and they *work in such a way that they are able to keep our blood pressure* within normal limits As is known these receptors and their nerves are working permanently as buffer nerves for our arterial blood pressure If they are eliminated immediately the systemic blood pressure rises from the normal level to a very high level from 120 mm Hg to perhaps 250–300 This shows that we all live in a condition of potential hypertension and if our blood pressure keeps *within normal limits it is because our moderator nerves are working* properly

These receptors were originally thought to be directly sensitive to pressure Later experiments showed that these so called baroceptors are not directly but indirectly sensitive to pressure They are located inside the arterial wall and are sensitive to stretching of the arterial wall so that any factor causing a change in the amount of stretching *of the arterial wall without any change in the pressure in the lumen* induces very marked reflex changes in the systemic arterial blood pressure An increase in the stretching of the arterial wall of the baro ceptive area brings down the systemic blood pressure while a decrease produces a marked rise in blood pressure

The question arises what could induce a change in the biological condition of the arterial wall so that the amount by which it is

stretched is altered as also the reaction of the arterial wall to the stretching which occurs when the arterial pressure rises This is a question which it is not possible to answer at the present time but I believe that we should seek some factor acting to decrease the active stretching of the arterial wall so that an increased pressure is necessary in order to restore the tension in the arterial wall to its previous level

The experiments of Page and Green have shown that what really happens in chronic hypertensive animals is that the threshold of the baroceptors to pressure is increased and I would suggest that the explanation is that the active stretching of the arterial wall has been decreased so that now more pressure is needed to stimulate the baroceptors than in normal conditions

We have studied chronic renal hypertensive dogs in whom after two or three months the blood pressure was about 220 mm Hg In these animals local application of noradrenaline to the baroceptive area increased the stretching of this section of arterial wall and immediately the blood pressure dropped from 220 to the low level of 50 the same response as in normal dogs The hypertension is rapidly reversible and indeed we would not expect a permanent increase of peripheral resistance to be produced by disturbance of the homeostatic mechanisms of regulation of blood pressure

DR J H GREEN (London) If we record from a single baroceptor fibre showing the impulse activity passing up the baroceptor nerve to the medullary centres in an animal with a normal arterial pressure of say 120 mm we find activity corresponding to each heart beat during systole and early diastole and then there is generally a pause and activity starts again with the next heart beat and so on If the pressure is very much higher e g 250 mm in a normal animal the activity is very much greater and may be steady throughout the whole cardiac cycle If the pressure is lower e g 80 mm activity is only in short bursts in early systole On the other hand in a hypertensive animal for instance one with chronic renal hypertension we find the normal activity at a high pressure of perhaps 250 mm and the levels of pressure producing increased or decreased activity are all correspondingly raised It is like re setting a thermostat It is reset so that in the chronic renal hypertensive state it looks as though the baroceptors now tend to keep the pressure at its new level

DR FLOYER One would anticipate that in an animal with chronic hypertension the baroceptor mechanism would become reset Dr Green has pointed out that the carotid sinuses give out a normal number of impulses at a higher level of pressure The work of Dr

Folkow and of others suggests that in hypertension the sympathetic contribution to vascular tone is normal this appears to exclude the possibility that a change in the sensitivity of the baroceptors alone could maintain the hypertension But it is possible, as Dr Heymans has suggested, that whatever affects the vascular tree and is respon sible for the increased peripheral resistance also affects the baro ceptors and lowers their sensitivity so that the whole cardiovascular system is stable with the blood pressure at a higher level

PROF McMICHAEL One factor that was put forward as a means of elevating the blood pressure was an increased strength of con traction of the heart I think that is a complete impossibility because the systolic pressure in the aorta entirely depends on its pressure volume relationships and the volume of blood put into the aorta at each beat The aortic run off (peripheral vascular resistance) determines the diastolic pressure There is no way in which the strength of the heart or strength of the contraction can be increased which would itself produce an elevation of pressure unless the baroceptors were completely out of action There are plenty of conditions in which the strength of the heart can be increased or the stroke volume increased such as hyperthyroidism or infusion of adrenaline (not noradrenaline) in these conditions the strength of contraction of the heart is increased but the blood pressure does not go up at all

It is often stated that it is the height of the blood pressure which determines arteriolar necrosis Arteriolar necrosis is a manifestation of an extreme degree of injury of the small vessels In addition to being determined or caused by experimental elevations of pressure it also occurs in certain conditions of arteritis in which there is no elevation of pressure I do not think that arteriolar necrosis is in fact purely and simply the result of an extreme elevation of pressure In fact we have been rather struck in looking at our pathological material with the frequency with which one sees arteriolar necrosis in the kidney in the territory of larger vessels in which the lumen is severely narrowed by onionskin endarteritis I think there are many points that can be raised against the hypothesis that arteriolar necrosis only results from high pressure There is some other damaging factor

DR LEDINGHAM I do not think the hypothesis that a more forceful contraction of the heart could be primary can be completely dis missed It is rather an extreme instance but I was thinking of the

possibility of local myogenic activity following Bayliss s suggestion and Dr Folkow s own work Admittedly their experiments were very short term ones but they do suggest that the smooth muscle of the arteriolar wall constricts as the perfusing pressure rises This is well known to happen in the renal vessels and Dr Folkow has also observed it in the vessels of the skeletal muscles

Surely it is conceivable that if the heart were to contract more forcibly the effect would be to rai e pressure and increase moment arily the cardiac output the myogenic activity would result in some degree of vasoconstriction of the peripheral vascular tree and the blood pressure might stabilize at a higher level This I agree is purely hypothetical but I do not think it can be ruled out completely

DR ZAIMIS I would like to comment on Dr Duff's results in connection with the different degrees of sensitivity of the blood vessels in hypertensives to adrenaline and noradrenaline Possibly his results can be explained in a different way We know that the blood vessels of skeletal muscles respond to adrenaline either by dilatation or constriction It may be that in hypertensives the more pronounced decrease of the blood flow is due not to an increased sensitivity of the vessels to the vasoconstrictor action of adrenaline but to the fact that the normal dilatation is prevented Such an explanation fits in better with Dr Folkow s hypothesis of a structural change in the wall of the vessels

DR DUFF I do not think that this suggestion would hold in the patients with comparatively early hypertension in whom there is no vascular narrowing so that one has to look for another explanation I suppose there are many possible explanations for the differential reaction to adrenaline and noradrenaline

PROF WILSON Regarding the relation of the anatomical lesions to the blood pressure in hypertension it is true that Dr Byrom and I postulated that a vicious circle might arise as a result of secondary hypertensive lesions but I feel one has to use extreme caution in arguing from structural changes to functional disturbances I think I stated that these arterial lesions are only the most obvious mani festation of a damaged kidney The really important thing is that experiment shows that this damaged kidney can certainly maintain hypertension The evidence does not show that this changed renal function is due to the actual structural l sions and I think we ought to keep our minds open about the possibility of functional changes in the kidney which can affect this regulatory function It is quite

obvious from Dr Floyer s experiments that an apparently normal kidney must have a changed function in relation to the production of hypertension Although *in the early stages of the experiment where one kidney is clamped there are no structural lesions in the un clamped kidney* it apparently has an altered function and I think that is a point on which more information is required

Dr Peart suggested that there was some doubt whether a vicious circle, in fact operates in chronic renal hypertension I believe his doubts *are based on the fact that removal of a diseased kidney in man may considerably lower the blood pressure even though arteriolar* necroses are present in the excised (and therefore presumably in the opposite) kidney I do not know how many arteriolar necroses are necessary to bring into operation the vicious circle or how much damage in the opposite kidney is necessary to make the process irreversible *The point is that in the rat some change does take place in the opposite kidney under the influence of hypertension* by virtue of which that kidney alone can then maintain hypertension In my view clinical and histological evidence supports the inference that a similar sequence occurs in man But it is only an inference and I am sure we should keep our minds open on this point

Regarding arteriolar necrosis being due to hypertension I should have thought the evidence is fairly clear that a high blood pressure is important in the production of arteriolar necrosis in hypertensive disease It is quite obvious of course that in polyarteritis nodosa rheumatic fever acute nephritis and collagen diseases arteriolar *necrosis may occur in the absence of hypertension That does not* mean that it is not produced by the same fundamental mechanism There may well be local vasoconstriction or some ischaemic process affecting the arterial wall in these diseases In terms of causative mechanisms we must distinguish therefore between arteriolar necrosis due to hypertension *on the one hand and that due to hypersensitivity* states on the other In malignant *hypertension* we cannot dissociate the occurrence of arteriolar necrosis from a high level of blood pressure or a sudden rise in blood pressure Endarteritis is of course a typical lesion of malignant hypertension and one must regard it I think *as the result again of a very high blood pressure* Fahr used to say in fact that endarteritis was the diagnostic lesion of malignant nephrosclerosis because in so many cases examined postmortem there was no arteriolar necrosis but only healed lesions and the outstanding vascular change was endarteritis

CHAIRMAN'S CONCLUDING REMARKS

I am sure all will agree that during this session we have had a fascinating series of communications of great interest to clinicians struggling with the problem of chronic hypertension A particularly hopeful sign is the recent increase in physiological studies on the peripheral circulation in man I think the rat is a most useful animal and ever since 20 years ago we introduced the tail plethysmograph technique for studying chronic hypertension experiments with rats have continued to yield most interesting results many of which are I believe directly applicable to human hypertension

On the other hand we obviously want to study hypertension in man The communications made during this session on changes in the peripheral resistance and on the problem of vessel responsiveness indicate how fundamental physiological techniques can be applied to the problem of human hypertension

I think this discussion in bringing together physiologists and clinicians has shown how much common ground there is It is quite remarkable how our various experiments widely differing in approach are apparently leading to the same kind of conclusion They are focusing attention on the peripheral vessels and there is less tendency to search for some renal pressor substance which acts on normal blood vessels I have always found it very difficult to believe that a damaged kidney functions better than a normal kidney It is also possible that the search for some local abnormality in the peripheral vessels in hypertension may throw light on the nature of physiological control of vascular tone

SUBJECT INDEX

SUBJECT INDEX

AUTHOR INDEX